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TRANSIENT METHEMOGLOBINEMIA FOLLOWING ADMINISTRATION OF AMMONIUM NITRATE

GEORGE B. EUSTERMAN AND NORMAN M. KEITH

GAMGEE, in 1868, demonstrated that amyl nitrite could cause methemoglobin to be formed in the blood. Since then it has been well recognized by many observers that nitrites may give rise to methemoglobinemia. However, there is very little in the literature indicating that nitrates may cause methemoglobinemia. A single reference by Binz and Gerlinger was found in which they stated that large doses of nitrates in animals may cause the formation of methemoglobin. Formerly nitrates were commonly used as diuretics, but because of the overemphasis of their possible toxic action, their use for this or other purposes had been practically abandoned in the last two decades. With the recent introduction of ammonium nitrate as an effective diuretic by one of us (Keith) in the treatment of various types of edema, the absence of toxic manifestations in a large number of patients was noteworthy even when the drug was given in large doses of 10 gm. daily. Christian and Barker and O'Hare recently reported cyanosis and methemoglobinemia in a patient with nephritis, who was receiving large doses of ammonium nitrate (15 gm. daily). Since May, 1928 we have observed the occurrence of cyanosis and methemoglobinemia in two patients who were receiving continuous diuretic treatment of ammonium nitrate and organic mercury compounds (merbaphen and salyrgan).

REPORT OF CASES

Case 1.—A man aged thirty-two entered the clinic April 23, 1928, with a presenting complaint of "stomach trouble." He had had two previous gastric operations elsewhere. He had had typhoid fever in childhood, the mother having died of the disease at that time. In 1918, ten years prior to admission, the patient gave a history characteristic of duodenal ulcer of a year's duration. In 1919, an operation on the stomach was performed, the nature of which was not determined, but presumably it was gastrojejunostomy. Three weeks later a recurrence of the original symptoms occurred, in addition to hematemesis and melena. For six years he had intermittent periods of gastric pain and the usual associated symptoms. In 1924 a second operation was performed, the nature of which was not known. This was followed by a period of complete relief for one and a half years. In 1926, the original symptoms, somewhat modified, recurred, with an increase in nausea, and vomiting of sour watery material. Since February, 1928 he had experienced daily gastric distress associated with abdominal distention. With a restricted diet and alkaline powders the symptoms were markedly relieved. A few days prior to admission the patient noticed slight edema of the feet and ankles and puffiness of the face, especially of the eyelids.

On general examination the patient was comfortable and appeared somewhat anemic. The teeth revealed considerable caries and moderate pyorrhea; the lungs, heart, blood pressure, temperature, and pulse rate did not show abnormalities. The abdomen was distended, with signs of shifting dulness, apparently in the flanks. The scars of previous operations were in a satisfactory condition, barring slight herniation in the lower third of the left rectus incision. The feet, legs, and scrotum were moderately edematous and the face appeared somewhat puffy. The superficial and deep reflexes were markedly reduced.

Hemoglobin was 67 per cent, erythrocytes numbered 4,030,000, the color index was 0.8+, and leukocytes numbered 6,400. The blood urea was 34 mg. for each 100 c.c. Tests of hepatic function were negative. The total gastric acidity was 80, free hydrochloric acid 70, and the contents removed measured 50 c.c. Fluoroscopic examination of the stomach revealed chiefly marked dilatation of loops of small bowel, apparently due to fluid in the abdomen. Tuberculosis was suggested by the roentgenologist as the cause. Later a cholecystographic examination was made and a diagnosis of nonfunctioning gallbladder with stones was reported. A tentative diagnosis of low-grade anasarca of indeterminate origin and recurrent peptic ulcer, probably at the anastomosis, was made and the patient was sent to the hospital for diagnostic observation and treatment, April 28. Urinalysis revealed albumin, graded 2 and a few casts.

Treatment by merbaphen, ammonium nitrate, and low salt and low fluid intake was promptly instituted. By May 7, ten days after admission to the hospital, the diuresis resulted in an output of 6,000 c.c. of fluid over the intake. The physical character of the abdomen had changed little and this aroused suspicion that there was some other factor accounting for the distention. The edema of the extremities and of the scrotum, however, had disappeared. A generalized gray, dry, ashen appearance of the skin, a bluish

color of the visible mucous membranes and of the hands and edges of the tongue was noted. At no time had there been a history of the use of coal tar products. At this stage the patient had received three intravenous injections of 1 c.c. each of merbaphen and 54 mg. of ammonium nitrate. Examination of the feces for occult blood was negative. Dyspnea was not present. The retina was definitely cyanotic. The blood urea, carbon dioxid combining power of the blood plasma and the blood chlorids were within normal limits. The blood withdrawn for these tests was of a chocolate color. That evening and during the early morning the patient was somewhat irrational and very weak, and fainted once. Spectroscopic examination of a sample of blood revealed the presence of methemoglobin. Arrangements were made to transfer the patient to the oxygen chamber without delay, if necessary. In the meantime withdrawal of all drugs and return to a normal diet was ordered. Within forty-eight hours the extreme cyanosis, which was especially marked May 8, had almost entirely disappeared. Two days later the patient's complexion was florid. At the outset, we suspected sulphemoglobinemia. Neither of us had ever previously seen such marked cyanosis disappear so rapidly and so completely (Table 1).

TABLE 1

JEJUNAL ULCER; ILEUS AND EDEMA OF SMALL BOWEL (CASE 1)

Date.	Comment.
4/23/28	Systolic blood pressure 115, diastolic 70; blood urea 34 mg. per cent; hemoglobin (Dare) 67 per cent; erythrocytes 4,030,000.
4/27/28	Blood urea 49 mg. per cent; serum bilirubin 0.3 mg. per cent.
4/28/28	Merbaphen 1 c.c., intravenously.
4/29/28	Ammonium nitrate, 6 gm., first day.
4/30/28	Diuresis, 3,700 c.c.
5/ 1/28	Blood urea, 28 mg. per cent.
5/ 2/28	Merbaphen 1 c.c., intravenously; diuresis, 2,450 c.c.
5/ 4/28	Merbaphen 1 c.c., intravenously; diuresis, 1,900 c.c.
5/ 7/28	Up to this a.m. total ammonium nitrate, 54 gm.; 3 c.c. merbaphen. Marked cyanosis.
5/ 8/28	Blood urea 38 mg. per cent; methemoglobin positive.
5/ 9/28	Slight cyanosis.
5/10/28	No cyanosis.

May 21, laparotomy was performed (C. H. Mayo) under local anesthesia The gallbladder and liver were found to be normal in appearance. There was no evidence of free fluid in the peritoneal cavity. Then, under general anesthesia the incision was enlarged and a general exploration was done. The original operation, done elsewhere, had been gastro-jejunostomy, without suture of the opening in the transverse mesocolon to the stomach. As a result of this all of the small intestine had herniated through this opening, causing marked edema of the bowel. To overcome this a second operation had been done elsewhere. This had consisted of anastomosis of the distended jejunum to the ileum 15 cm. above the ileocecal valve without reducing

the hernia. C. H. Mayo disconnected the anastomosis between the jejunum and ileum and closed the openings in both jejunum and ileum. Examination of the existing gastro-enterostomy opening disclosed the presence of a jejunal ulcer. The hernia was reduced, the gastro-enterostomy was disconnected, the jejunal ulcer excised, and the openings in both the stomach and jejunum were closed. Thus the normal continuity of the gastro-intestinal tract was reëstablished. Next, because of the edema of the small intestine and for the purpose of feeding, jejunostomy was done, and a fenestrated tube inserted into the lumen of the jejunum. This tube was passed upward beyond the sites of the two previous openings in the wall of the intestine, and the end of the tube was brought through the omentum out of a stab wound in the abdominal wall. The scar of a healed duodenal ulcer was present about 0.5 cm. below the pylorus. The patient made a fairly uneventful recovery and was dismissed June 5.

Aside from the occurrence of methemoglobinemia as a complication, this case presented other features of clinical interest. In the first place, a distended, edematous small bowel can simulate abdominal ascites. In all previous cases of a similar nature we do not recall a single one in which the physical signs so closely simulated those seen in ascites. In all probability the commonest instances of this kind follow gastro-enterostomy where, through imperfect closure or failure of closure of the rent in the transverse mesocolon, a portion or all of the small bowel may herniate through this rent producing obstruction of the proximal part of the jejunum. The recurrence of symptoms soon after the first operation, in addition to hematemesis and melena which had not obtained previously, is highly suggestive of a recurrent ulcer in a new situation, especially at or below the site of the anastomosis. It was this fact that finally made us advise another exploration.

This case is also an example of how the laboratory investigations, even when carried out by experts, may mislead the clinician. The roentgenologic impression of the presence of fluid in the abdomen, the cholecystographic data positive for a diseased gallbladder containing stones, and the failure to visualize the jejunal lesion by fluoroscopic examination, all were disconcerting in the light of the revelations at the operating table. The hyperacidity and the fluoroscopic evidence of marked dilatation of loops of small bowel were the only laboratory data consistent

with the pathologic process. Of course the postoperative complication, which was aggravated by a short-circuiting operation of the small bowel made the case a very unusual one and gave rise to physical conditions which made diagnosis extremely difficult. The peripheral edema probably was due to a low grade renal involvement.

Case 2.—This patient was a woman aged forty-seven years. She was admitted to the clinic June 11, 1928. Her chief complaint was swelling of the legs and abdomen for the last three years. She had had acute rheumatic fever at the age of fourteen years, and "congestion of the lungs" at twenty. She had been married three times, but never had been pregnant. The illness began three years before admission with severe cough, dyspnea, swelling of the abdomen, dependent edema and oliguria. Hospital treatment at that time included restriction of fluids, electric baths, and abdominal paracentesis. After treatment for one month the edema and ascites were greatly reduced. The patient had felt fairly well since and had been able to do some of her housework, but had not been entirely free from edema and ascites. Ten days previous to examination, all symptoms became more marked and continued so until the time of admission. Constipation had been present throughout, and salts had been taken frequently.

The patient appeared slightly anemic; the sclerotics were clear. There was ascites, graded 4, and dependent edema, graded 3. The percussion note was impaired over the bases of both lungs posteriorly, more noticeably on the left. The heart was not enlarged, the action was regular and murmurs were not present. A gross pathologic lesion could not be demonstrated in the pelvis. A right inguinal hernia was present. A roentgenogram of the chest showed definite pleural thickening of the left lower part of the chest, which was thought possibly to be due to previous pleurisy. Repeated examination of the sputum failed to show any bacilli of tuberculosis. A single stool examination was negative for acid-fast bacilli. Routine examinations of the urine did not show anything abnormal and renal function was satisfactory. Hemoglobin (Dare) was 62 per cent, erythrocytes numbered 3,270,000 and leukocytes 4,900; the differential count was normal. An electrocardiogram showed inversion of the T waves in leads I and II, but a second tracing two weeks later was essentially negative. The Wassermann reaction was strongly positive on two occasions. Test of hepatic function did not show dye retention and the serum bilirubin was 0.3 mg. for each 100 c.c. The course while the patient was in the hospital for seven weeks was practically afebrile throughout. Periodically there was marked constipation. This was subsequently relieved by regularly repeated doses of milk of magnesia. On account of the great discomfort from the marked ascites, abdominal paracentesis was carried out soon after admission. This was repeated several weeks later. On both occasions, the ascitic fluid had the appearance of milk. Straw-colored, clear fluid was removed from the right pleural cavity on two occasions. Besides the direct removal of fluid from the peritoneal

and right pleural cavities, diuretic treatment was early instituted. This consisted of the use of a weighed low-fluid, low-salt diet, of ammonium nitrate, calcium chlorid, the organic mercury compound, salyrgan, and the caffeine preparation, euphyllin (theophylline and ethylenediamine). These diuretic substances were periodically combined in order to give a maximal dehydrating effect. On the combined treatment by diet, paracentesis, and diuretics, the patient's weight was reduced from 157 to 100 pounds, but at the time of dismissal there was still evidence of ascites, fluid in the pleural cavities, and dependent edema, although much less than on admission. During two periods when ammonium nitrate and salyrgan were being administered, a moderate degree of cyanosis developed. The cyanosis was first observed while the patient was sitting up in bed eating her evening meal. There was no apparent increase in the respiratory symptoms nor did the patient feel subjectively any worse. The blood during both periods of cyanosis was examined spectroscopically and methemoglobin demonstrated. The

TABLE 2

CHRONIC POLYSEROSITIS? (CASE 2)

Date.	Comment.
6/12/28	Systolic blood pressure 140, diastolic 90; blood urea 37 mg. per cent; hemoglobin (Dare) 62 per cent, erythrocytes 3,270,000; salyrgan 0.5 c.c., intravenously.
6/13/28	Serum bilirubin, trace; abdominal paracentesis, 7,000 c.c. milky fluid; ammonium nitrate, 8 gm. daily, begun.
6/16/28	Serum bilirubin, 0.3 mg. per cent.
6/21/28	Salyrgan 1 c.c., intravenously.
6/25/28	Salyrgan 1 c.c., intravenously.
6/28/28	Cyanosis, graded 2; ammonium nitrate 89 gm. since June 13; paracentesis of right side of chest, 850 c.c. straw-colored fluid.
6/29/28	Cyanosis, graded 1.
6/30/28	Ammonium nitrate, 10 gm. daily, begun. No cyanosis.
7/ 3/28	Salyrgan 1 c.c. intravenously.
7/ 5/28	Methemoglobin positive; cyanosis, graded 1; ammonium nitrate, 56 gm. since June 30, 145 gm. since June 13.
7/ 6/28	Right pleural paracentesis, 400 c.c. straw-colored fluid.
7/10/28	Cyanosis, graded 2; salyrgan 1 c.c. intravenously; ammonium nitrate since July 6, 32.5 gm., 177.5 gm. since June 13.
7/14/28	Abdominal paracentesis, 4,000 c.c. milky fluid.
7/16/28	Methemoglobin negative.
7/19/28	Methemoglobin negative.
7/23/28	Salyrgan 1 c.c., intravenously; total 5.5 c.c.
7/24/28	Methemoglobin negative; began ammonium nitrate. No cyanosis.
7/26/28	Cyanosis, graded 1.
7/27/28	Methemoglobin positive; cyanosis, graded 1; total ammonium nitrate since July 24, 24 gm.
7/28/28	Cyanosis, graded 1; total ammonium nitrate since June 13, 207.5 gm.

cyanosis rapidly disappeared when diuretics were discontinued. These two diuretics were deliberately administered on the second occasion to determine whether they could cause cyanosis and methemoglobinemia. One cubic centimeter of salyrgan produced marked diuresis but did not produce cyanosis or methemoglobinemia, but 10 gm. of ammonium nitrate given daily produced on the third day, after 24 gm. had been taken, both cyanosis and methemoglobinemia. As in the previous cyanotic period, untoward symptoms did not develop. Thus, ammonium nitrate in distinctly different amounts produced in this case definite methemoglobinemia on two occasions. The clinical diagnosis was: tertiary syphilis, possibly cirrhosis of the liver or chronic polyserositis, or Pick's disease (Table 2, p. 1494).

COMMENT

From the observations in Case 2, the available evidence strongly points to ammonium nitrate as the primary etiologic factor. On the basis of these experiences, one of us (Keith) has given intravenously comparable amounts of ammonium nitrate singly and combined with organic mercury compounds to two normal dogs and methemoglobinemia has not resulted. Ammonium nitrate has been given in large doses to normal men and to a great number of patients with different types of dropsy, in The Mayo Clinic, during the last three years, and cyanosis with methemoglobinemia occurred in only these two patients.

The pathologic processes found in these patients were so divergent that accurate inferences could not be drawn from this standpoint as to the real mechanism involved. However, in Case 1 there was actual evidence of dysfunction of a large portion of the small bowel; in Case 2 severe chronic constipation was a distinct clinical feature, especially during the first period of methemoglobinemia. From these observations one might conjecture that some intestinal dysfunction could be a factor in causing abnormal metabolism of nitrates.

The methemoglobinemia of nitrate poisoning, more prevalent two decades ago, when large amounts of bismuth subnitrate were used for diagnostic purposes, was more prompt and severe after rectal administration, especially in patients suffering from intestinal putrefaction. It occurred less frequently, and in milder degree, when suppurating sinuses were injected with the paste.

These rare and interesting occurrence of methemoglobinemias after ingestion of nitrates bring up the question of the abnormal chemical action involved. Its production is probably due to reduction of the nitrate to nitrite by some abnormal reaction within the body.

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TREATMENT IN A CASE OF POLYCYTHEMIA VERA

HERBERT Z. GIFFIN

A WOMAN aged thirty-one years came under observation June 15, 1925. Six years previously she had begun to have pain in the epigastrium and in the left upper quadrant, and also suspected at that time that an enlargement was present in the left side of the abdomen. The attacks of pain would come on suddenly, were quite severe, lasted about a day, and were accompanied by nausea and vomiting; they recurred at intervals of several weeks. Three years previous to examination the attacks became associated with severe frontal headache, vertigo, and "specks of fire" before the eyes. Two years previously an abdominal exploration was done elsewhere at which time the gallbladder and appendix were removed. Following the operation the attacks continued as before.

Examination disclosed the high color of polycythemia vera with a considerable degree of generalized pigmentation of the skin. The spleen extended almost to the umbilicus. The eye-grounds showed some engorgement of the retinal arteries. Erythrocytes numbered 6,890,000, and the leukocytes 7,500. The hemoglobin was 19.4 gm. for each 100 c.c. (normal 15.7 gm.). The differential count showed nothing of especial importance. The platelet count was 148,000. The bleeding time was normal. Tests of hepatic function did not show dye retention. The serum bilirubin was 1.5 mg. The blood volume was 176 c.c. for each kilogram (normal 87.7 c.c.), and the plasma volume was 48 c.c. for each kilogram (normal 51.2 c.c.). The hematocrit showed 71 per cent cells and 29 per cent plasma.

Under observation in the hospital the patient was given a course of phenylhydrazin hydrochlorid in doses of 0.1 gm. three times a day for a period of thirteen days; the total dosage was 3.8 gm. During the course of treatment there was a gradual increase in the serum bilirubin from 1.5 to 7.7 mg., together with the appearance of hematin in the serum. Associated with this there was a large output of urobilin in the urine. The van den Bergh reaction was consistently indirect. The spleen and liver became enlarged and the spleen became tender as icterus developed; the general aspects were those of active hemolysis. When treatment was discontinued the erythrocytes numbered 5,820,000; one week later they numbered 4,200,000, and two weeks later 2,240,000 while the hemoglobin decreased to 8.7 gm. and the leukocytes increased to 15,000. Unnecessarily severe anemia had evidently been produced by the cumulative action of the phenylhydrazin. The blood volume three days after the discontinuance of the drug became reduced to 104 c.c. for each kilogram, and the hematocrit showed complete reversal of the former figures: 37 per cent cells and 63 per cent plasma. Tests of hepatic function

did not show evidence of dye retention. Blood urea became increased to 69 mg., uric acid was 2.5 mg. and creatinin 1.5 mg. for each 100 c.c. Urinalysis showed only a trace of albumin, and the phenolsulphonephthalein return was consistently normal. A slight increase in the resistance of the erythrocytes was noted at the first examination, and during the period of anemia it was still present. Clinically the patient was markedly improved in spite of jaundice and anemia. The liver and the spleen became smaller, pain and headache disappeared, and the patient felt quite strong.

One month after treatment had been discontinued the erythrocytes had risen to 3,610,000 and the hemoglobin was 60 per cent (Dare). The spleen extended only 2 cm. below the costal margin. The patient's general condition at the time of dismissal, July 31, 1925, was better than it had been in years. For a period of about two months her condition was very satisfactory. She had a few mild headaches, and the abdominal pain had entirely disappeared. Following this the symptoms gradually recurred and nine months after dismissal a second course of phenylhydrazin was necessary. Following this course the patient was again in satisfactory health for approximately a year when a third course was given. In the intervals between the courses of treatment phenylhydrazin was not used.

COMMENT

This case illustrates one method by which phenylhydrazin hydrochlorid may be administered in a severe case of polycythemia vera. In a series of forty-one patients with polycythemia vera treated by means of phenylhydrazin, twenty-five may be said to have obtained satisfactory results. Patients who had been ill for a long time, with advanced arteriosclerosis and visceral disease, were able to reduce their blood volume but other factors prevented a return to satisfactory health. It is necessary to adapt the treatment to the individual case, and experience indicates that large daily dosage is not as a rule necessary. Many of the patients, after an initial course of treatment similar to the one given in this case, have remained free of symptoms on doses of 0.1 to 0.3 gm. each week and subsequent courses of daily administration have not been necessary. Others have voluntarily stated that they do much better on the administration of a small dosage of phenylhydrazin each week than on a series of daily doses.

Reports in the literature concerning the treatment of polycythemia vera by means of phenylhydrazin have been favorable. In the early cases, not infrequently unnecessarily severe anemia

was produced and the occurrence of peripheral thrombosis was noted. The anemia, however, quite consistently disappeared rapidly following discontinuance of the drug. Experimental work likewise has not shown definite evidence of toxicity, although it has not been proved that impairment of the function of the kidneys does not occur; there does not seem to be hepatic injury with dosages considerably larger than those used in man.

Bryan has called attention to the possible serious effects of phenylhydrazin. In 1927 he reported the case of a woman aged sixty-five years with advanced arteriosclerosis and evidence of hepatic, splenic, and renal injury, in whom a total dosage of 2.9 gm. of phenylhydrazin was followed by a rapid reduction in erythrocytes. The patient became comatose and died sixteen days after the beginning of treatment.

A case similar to Bryan's has occurred in my experience; in two other cases extensive thrombosis developed involving the larger vessels, following a dosage of phenylhydrazin which was not excessive, respectively 1.5 and 4 gm. All of these patients were more than sixty years of age and had an advanced type of the disease, including very marked vascular and visceral changes.

Although it is recognized that the treatment of polycythemia vera by means of phenylhydrazin is more effective than any other method of treatment, this experience has led to caution in the administration of phenylhydrazin. Patients with advanced polycythemia vera of a grade necessitating confinement to bed are now treated by other methods. Extreme caution is observed in the administration of phenylhydrazin to patients more than sixty years of age and to patients who show extensive arteriosclerosis and evidence of visceral injury, even though the patient is ambulatory. In these cases it is customary to give 0.1 to 0.2 gm. only, in order to observe the effect over several succeeding days. Moreover, patients who have had thrombosis are treated cautiously, because it is the impression that extensive thrombosis is more likely to develop during treatment. Treatment is best carried out as an ambulatory regimen with every effort made to keep the circulation free. When an initial course of daily treatment is necessary, a total initial dosage of 1.5 to 3.5

gm. is usually sufficient; subsequent dosage can be determined by the patient according to his symptoms, and usually from 0.1 to 0.3 gm. of phenylhydrazin each week will maintain the patient in comfort. If an initial daily course of treatment has not been given in less advanced cases which are not under close observation, the administration of 0.1 gm. of phenylhydrazin a week may bring about improvement; the dosage may gradually be increased if necessary to 0.3 gm. a week.

THE DIFFERENTIATION OF PRIMARY CARCINOMA OF THE BRONCHUS AND UNUSUAL TYPES OF PULMONARY TUBERCULOSIS

PORTER P. VINSON

THE symptoms and the laboratory, clinical, and roentgenologic data in the average case of pulmonary tuberculosis are classic and yet in many instances distinction of this disease from some of the rarer types of pulmonary disorders is exceedingly difficult, particularly in the presence of the very unusual infiltrations, tuberculous in origin, near the hilum of the lung.

A marked increase has been observed in the incidence of primary carcinoma of the bronchus during the last few years. If there is an infiltration near the hilum radiating with decreasing density into the substance of the lung, carcinoma should be the first consideration. Tuberculosis does not usually produce narrowing of a large bronchus and therefore one rarely observes signs of bronchostenosis, whereas in carcinoma bronchial occlusion is the rule and signs indicating bronchial obstruction are frequently present. However bronchostenosis may not exist in carcinoma and there may be evidence of occlusion of the bronchus in tuberculosis. More significant is the observation on bronchoscopic examination of the presence of an ulcerating lesion in the bronchus in cases of carcinoma and negative observations or simply partial stenosis without ulceration in cases of tuberculosis.

It is not usually advisable to recommend bronchoscopy if patients are suffering from pulmonary tuberculosis, but the cases reported here will serve to illustrate the fact that primary bronchial malignancy may develop in cases of tuberculosis in which it is necessary to remove tissue for diagnosis and in which a lesion may resemble carcinoma and yet the positive or pre-

sumptive bronchoscopic evidence may aid in the establishment of a diagnosis of tuberculous disease of the lung.

REPORT OF CASES

Case 1.—A woman aged sixty-four years was examined March 21, 1927. Six months previously she had been in bed for three weeks with influenza and following this noticed soreness in the posterior portion of the chest on the right side. She had lost 6 pounds in weight. Cough or fever had not been noted at any time. She complained of a lump in the throat of thirteen months' duration, and pain in the lower lumbar region that had been present at intervals of six months to a year for fifteen years.

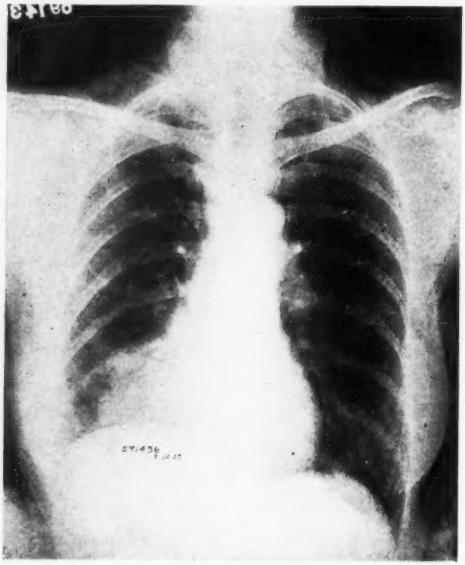

Fig. 233.—Area of infiltration in base of the right lung thought to be due to bronchiectasis.

General examination of the chest revealed an area at the base of the right lung posteriorly where the breath sounds were very distant and the percussion note was markedly impaired. Roentgen-ray examination of the chest revealed an old lesion in the upper lobe of the right lung and an area of infiltration at the base of the right lung that was thought to be due to bronchiectasis (Fig. 233). Bronchoscopic examination showed the bronchi to the lower lobe of the right lung to be markedly stenosed and to exude a moderate amount of purulent material.

The patient was instructed to return for examination in three months, but she failed rapidly and returned in three weeks (Fig. 234). It was then believed that the pulmonary lesion was malignant, and a specimen of tissue was removed bronchoscopically from a bronchus of the right lower lobe. Microscopic examination showed this to be tuberculous in character (Fig. 235). The sputum was negative for bacilli of tuberculosis. The patient died April 28, 1927.

Case 2.—A woman aged twenty-eight years came for examination February 8, 1926. She had been well until three weeks previously when a sore throat with a cold developed. Associated with this was pain in the

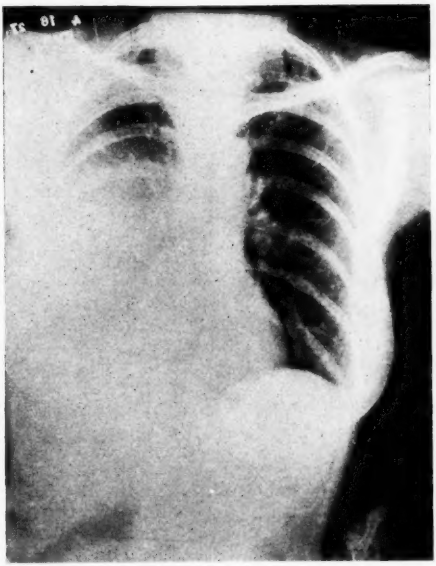

Fig. 234.—Same case as that shown in Fig. 233. Marked increase in density is shown on the right side.

left side of the chest, increased on deep breathing and diagnosed pleurisy by her physician. There was some elevation of temperature. She was confined to bed for four days. Four days before she came to the clinic, swollen, indurated, painful, red lesions appeared over both shins and the right thigh.

The general examination was essentially negative, save for the lesion of the skin which was diagnosed erythema nodosum. However, roentgenograms of the chest revealed an area of consolidation in the region of the left hilum that resembled primary carcinoma of the bronchus (Fig. 236). The sputum was repeatedly negative for the bacilli of tuberculosis. The patient

was kept under observation for six weeks and at the end of that period symptoms had increased with evidence of left pleural effusion (Fig. 237), and a firm lymph node had appeared in the left supraclavicular region. Bronchoscopic examination did not disclose evidence of an intrabronchial lesion. The lymph node was removed and was found to be tuberculous (Fig. 238); the effusion was a clear serous type. The patient was then admitted to a tuberculosis sanatorium and in seven months was symptomatically well. The roentgen-ray examination of the chest at that time was negative (Fig. 239), and the patient has remained well.

Case 3.—A man aged fifty-nine years came for examination June 27, 1927, complaining of a mild dry cough of two years' duration. Eight months

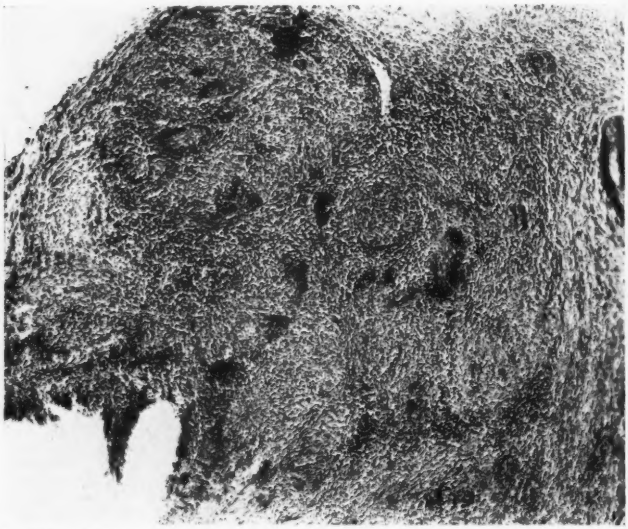

Fig. 235.—Section of tissue removed from the bronchus, showing typical tuberculous lesion.

previously, the cough had increased in severity and was associated with expectoration and pain in the right side of the chest radiating into the right shoulder. During the last five weeks of the illness, the afternoon temperature rose to 101° F. Besides the pulmonary symptoms, the patient experienced considerable difficulty in urinating for a period of two years. This was attributed to benign hypertrophy of the prostate gland. There was a loss of 8 pounds in weight. A diagnosis of primary carcinoma of the right bronchus had been made by the physician at home.

Examination showed impairment of the percussion note in the interscapular region on the right side without alteration in the breath sounds.

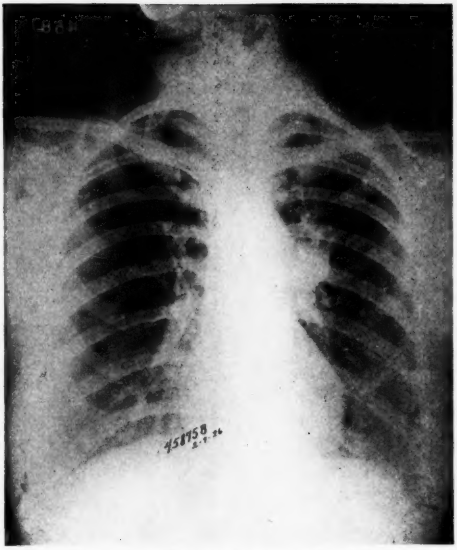

Fig. 236.—Lesion in the area of the left hilum resembling primary carcinoma of the bronchus.

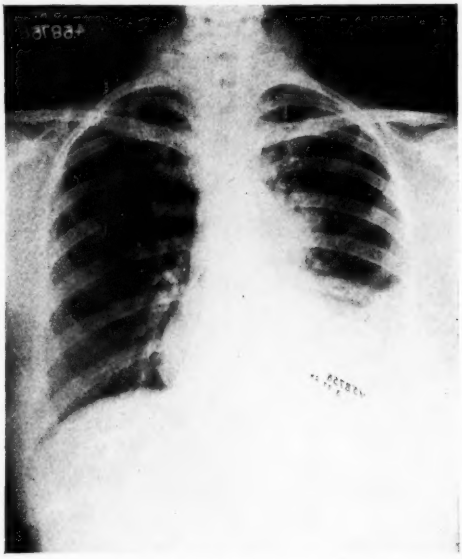

Fig. 237.—Same case as that shown in Fig. 236. The original shadow is not increased but pleural effusion is shown at the base of the left lung.

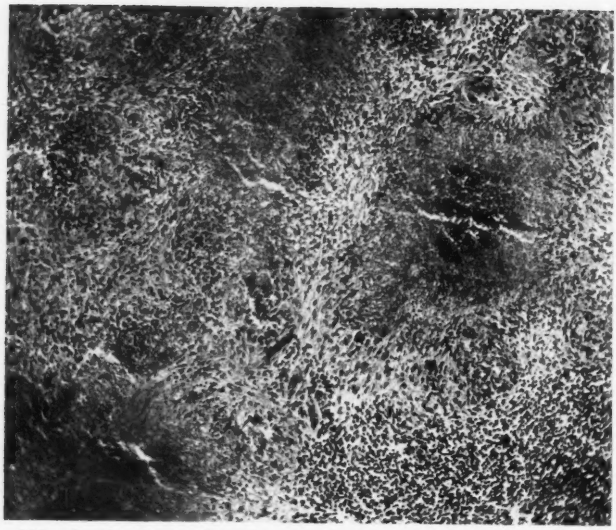

Fig. 238.—Section from tuberculous gland removed from the left supraclavicular region.

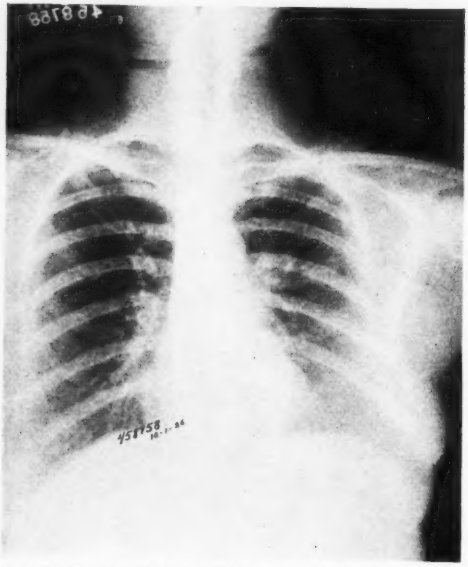

Fig. 239.—Practically complete resolution of the shadow of the left hilum, and absorption of pleural effusion.

The prostate gland was slightly enlarged. Roentgen-ray examination revealed infiltration in the third interspace on the right side near the hilum with interlobar pleurisy (Fig. 240). Examination of the sputum for bacilli of tuberculosis was negative. On bronchoscopic examination, pus was seen exuding from the mesial division of the bronchus of the right lower lobe. There was no evidence of ulceration or of bronchial obstruction. Smears were made of the secretion obtained from the bronchus, but bacilli of tuberculosis were not found. Because of the negative bronchoscopic data, it was thought advisable to assume that the lesion was tuberculous and the patient was referred to a tuberculosis sanatorium. During the next five months, his general condition improved very much, and he gained 13 pounds.

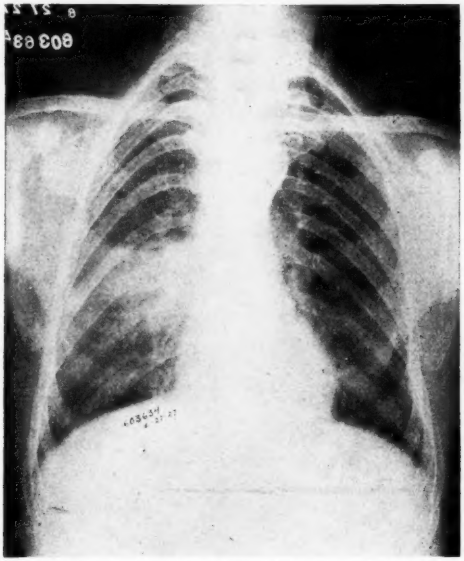

Fig. 240.—Infiltration at the hilum of the right lung, thought to be malignant in nature.

In the early part of November, 1927, urinary symptoms became severe and December 5, he returned to the clinic for further consideration. The general examination was essentially the same as before but the roentgenograms of the chest had changed entirely, and resembled the type of infiltration seen in tuberculosis (Fig. 241). The sputum failed to reveal the organisms of tuberculosis, but it was assumed that the pulmonary disease was tuberculous in nature. Treatment was advised for the prostatic obstruction and the patient was advised to return to the sanatorium for prolonged observation.

Case 4.—A man aged fifty-one years came for examination July 21, 1928. One brother had pulmonary tuberculosis. Sixteen years previously the patient had become ill, with cough, expectoration, fever, and loss of weight. Bacilli of tuberculosis were found in the sputum. After six months in a sanatorium, he improved, but three years later symptoms recurred necessitating further treatment. His general health was then good until March, 1928, when cough again developed, with expectoration, fever, pain in the right side of the chest radiating down the right arm, and loss of weight and strength. Bacilli of tuberculosis were again demonstrated in the sputum by the physician at home.

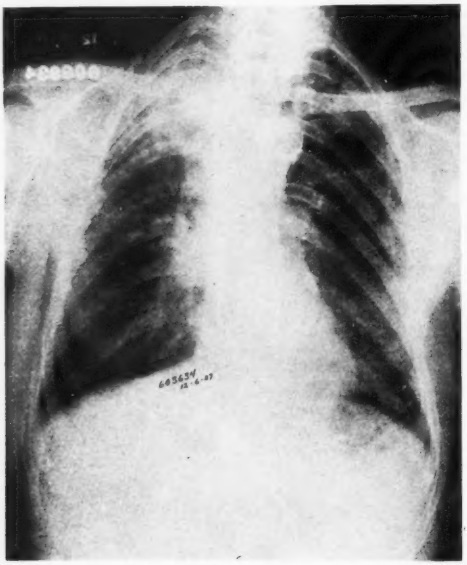

Fig. 241.—Marked infiltration in the upper lobe of the right lung radiating from the hilum, evidently tuberculous in nature.

General examination of the chest revealed marked dulness with markedly distant breath sounds over the upper lobe of the right lung anteriorly. Roentgen-ray examination of the chest revealed a large circumscribed nonpulsating tumor in the upper portion of the chest on the right side with pleuritic thickening at the apex (Fig. 242). The sputum was examined repeatedly for bacilli of tuberculosis and on one occasion a clump of suspicious-appearing organisms was found. All of the diagnostic data were in favor of tumor, but because of the history of tuberculosis it was thought that a thickened tuberculous pleura or a localized pleural effusion was responsible for the

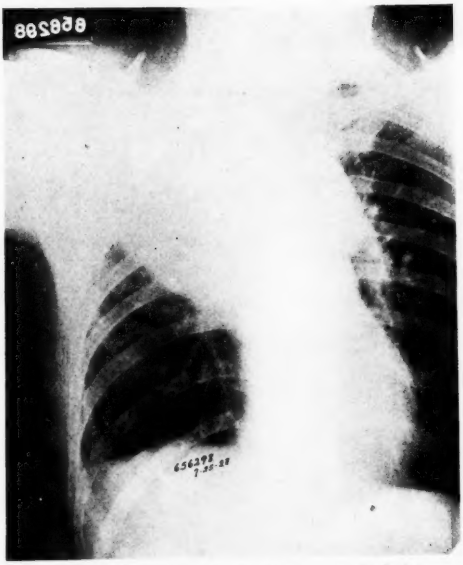

Fig. 242.—Roentgenogram taken on admission.

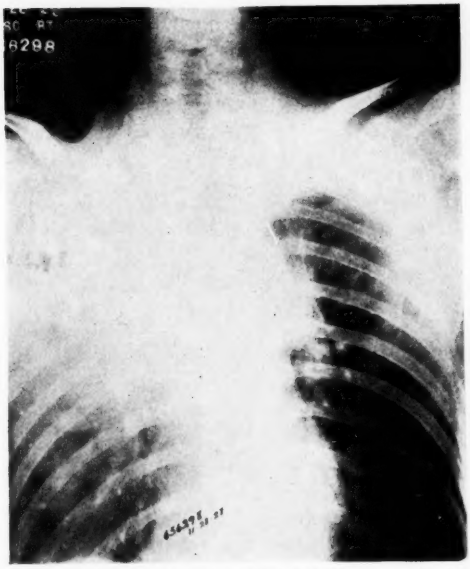

Fig. 243.—Same case as that shown in Fig. 242, four months later, showing increase in extent of lesion.

symptoms. Diagnostic aspiration of the right side of the thorax was negative. Bronchoscopy was considered but was not advised.

The patient went home but because of increasing symptoms returned for examination November 28, 1928. At that time, there was a marked

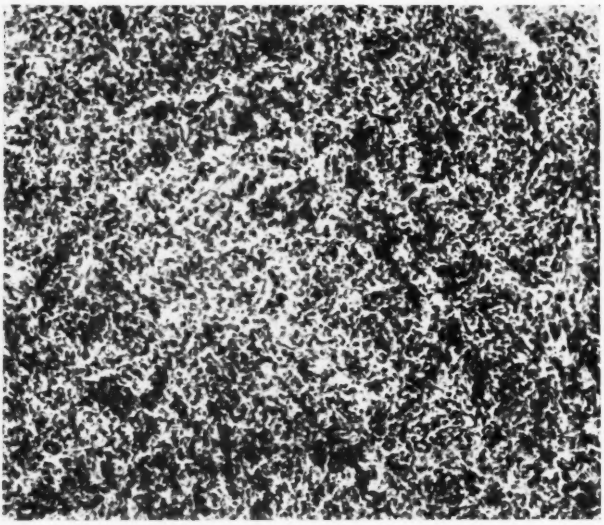

Fig. 244.—Tissue removed from the lesion in the right main bronchus.

increase in the clinical and roentgenologic data, and bronchoscopy was performed (Fig. 243). A bleeding, ulcerating, granular, pale lesion was found in the right main bronchus, and tissue removed for microscopic examination revealed carcinoma, graded 4, probably adenocarcinoma (Fig. 244).

OSTEOPOROSIS SECONDARY TO HYPERTHYROIDISM

HAROLD F. DUNLAP AND ALEXANDER B. MOORE

AUB and his coworkers at the Massachusetts General Hospital reported, in 1926, some investigations conducted on the influence of the thyroid gland on the metabolism of calcium. The patients selected for study were given a carefully weighed diet deficient in calcium (0.1 gm. each day) but of sufficient calorie requirements. Determinations at three-day intervals were made on the total output of the calcium, phosphorus, and nitrogen in the urine and feces. Frequent determinations were also made of the calcium and phosphorus content of the blood and of the basal metabolic rate. A negative calcium balance (greater output than intake) was found in all the patients on this regimen and the total quantity of calcium excreted varied in proportion to the height of the basal metabolic rate. Thus, in cases of hyperthyroidism dependent either on exophthalmic goiter or adenomatous goiter with hyperthyroidism, and in normal subjects whose metabolism had been raised by the administration of thyroid extract or thyroxin, the quantity of calcium excreted was high as compared to that excreted by the control subject. As the basal metabolism approached a normal level, either following operation or on the administration of compound solution of iodin (Lugol's solution), the amount of calcium excreted fell to a value approaching that of the quantity excreted by the control subject. As illustrative of this, they cited one case of severe exophthalmic goiter in which the basal metabolic rate was high, and the total calcium output was five times as great as that of a control subject. Conversely, in myxedema and tetany calcium excretion was lowered as compared to a control subject. The excretion of phosphorus behaved in a similar manner, although to a lesser degree. In all cases studied, excluding the cases of tetany, in which the blood calcium was

lowered because of lack of the specific parathyroid hormone, the determinations of the blood values of calcium and phosphorus were normal.

As there was a negative calcium balance in the cases studied it is quite obvious that the increased excretion of calcium in the cases in which basal metabolic rates are elevated must be of endogenous origin. The only known large reservoir for calcium storage in the human body is in the osseous system. It has been proved that the calcium values of the blood and vital tissues of the body are the most constant of all metals. According to Corlett, the osseous system is able to withstand considerable drainage on the calcium supply without any deleterious effects except slight weakness, whereas drainage on the calcium supply of the more vital tissues of the body would result in rapidly approaching death. He reported on a somewhat similar condition produced in experimental animals in which a negative calcium balance developed when the condition occurred as a result of deficiency of vitamin D in the presence of a sufficient calcium intake. This condition may be obviated by supplying vitamin D. He has named this state calcium diabetes. The mode of production here, however, is different from that produced in disturbance of the thyroid gland, as these patients were on a diet containing adequate calories, and an adequate supply of vitamins. In order to show the osseous changes occurring in these cases of disturbance of the thyroid gland, roentgenologic studies of the bones were conducted by Aub and his associates as well as by W. A. Plummer. Additional observations at The Mayo Clinic are reported herewith.

As seen with the roentgen rays, osteoporosis from hyperthyroidism affects all the bones, but when of moderate or slight degree it is most readily discerned in the spongy bones and those with superficial coverings, such as the skull, ribs, and bones of the extremities. In the long bones it is likely to be most apparent in the epiphyses and ends of the diaphyses. The loss of calcium varies in degree from mere increase of translucence, so trivial that it may escape notice, to marked and unquestionable rarefaction. In the slighter cases a change is not visible except

diminution of density of the bone shadow. When absorption is pronounced, the shadow is quite faint, the trabeculæ are not clearly defined and the bone appears rather structureless. If marked, the rarefaction will be apparent in routine roentgenograms for other purposes, but if slight the demonstration requires comparison with control subjects. This is best accomplished by simultaneous roentgenography of the patient and a control subject of approximately the same age, weight, and physical activity. The hands furnish the most practical criterion, for one of the patient's hands and one of the subject's hands can be exposed simultaneously on the same film, thus assuring the same technical factors. For comparison of other bones, when those of patient and subject cannot be shown on one film, an identical technic must be employed for both.

Numerous diseases and conditions giving rise to osteoporosis may enter into the differential diagnosis. Among them are local or general nonuse, neural or vascular trophic disturbances, infection, bone atrophy, osteomalacia, and malignant metastasis. Osteoporosis resulting from local nonuse, localized trophic changes or infection is restricted to a single bone or the bones of one limb; when other bones, especially homologous bones, are also exhibited and appear normal, roentgenologic evidence is afforded for the exclusion of osteoporosis from hyperthyroidism. In true atrophy the bone is not only rarefied but shrunken. Osteomalacia, a disease chiefly of parturient women, affects particularly the pelvis and spine, often with striking deformity. Metastatic malignant lesions are revealed as more or less discrete, translucent areas which ordinarily have little resemblance to the diffuse rarefaction of osteoporosis; at times, however, if the roentgenogram is limited in scope, distinction is difficult. On the whole, in most cases of osteoporosis of hyperthyroidism the roentgenologist's first information is derived solely from the film of a single part, and he can only report the rarefaction without attempt to surmise its cause. When osteoporosis is reported it is therefore incumbent on the clinician to canvass the possible causes of the condition and if necessary call for further roentgenologic studies and laboratory tests.

Experience thus far indicates that the degree of decalcification is in direct ratio to the severity and duration of the hyperthyroidism, and is usual rather than unusual. This is substantiated in the five cases here recorded. In the first case the hyperthyroidism, although severe at the time of admission, had not been prolonged, and in the second case hyperfunction of the thyroid gland had existed only a year. In both cases the osteoporosis was only moderate at most. The last three cases exemplify an intense and long-enduring hyperthyroidism with a pro-

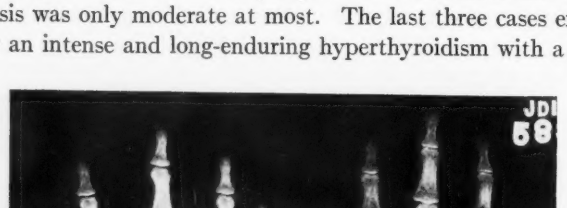

Fig. 245.—(Case 1.) Marked porosity of the bones of the hand as compared with the control subject on the left.

portionate absorption of calcium, the latter being so pronounced that the question of metastatic malignancy was raised in two of the three cases.

Case 1.—A girl aged twenty years, who was suffering severely from exophthalmic goiter, was hospitalized immediately because of crisis at the time of admission. She had noted enlargement of the thyroid gland seven years previously, and for three years before coming to the clinic had had definite symptoms of hyperthyroidism. The basal metabolic rates ranged from

+74 on admission to +55 previous to thyroidectomy. Owing to the severity of the hyperthyroidism, injection of hot water and single ligation were carried out as test measures prior to thyroidectomy. The pathologist's report was hypertrophic parenchymatous thyroid gland. Roentgenographic examination of the hands revealed decreased density of the bones as compared to those of the control (Fig. 245).

Case 2.—This patient was aged twenty years. She gave a history of hyperthyroidism of one year's duration. The basal metabolic rate was never below +70 previous to operation. Several injections of hot water were given and ligations were carried out. Roentgenograms of the bones showed increased translucence of the bones of the hands and wrists as compared to to the control subject.

Case 3.—A woman aged fifty-three years registered at the clinic December 3, 1927. She had first noticed a goiter thirteen years previously. During the following year she had lost 30 pounds in weight. A voracious appetite, exophthalmos, and gastro-intestinal crisis developed, and she became very nervous. During the last ten years she had noted palpitation, tachycardia, occasionally pretibial edema, intolerance to heat, and constant tremor. At the time of examination, the weight was 103 pounds. The usual weight prior to the development of the goiter had been 150 pounds. The blood pressure was 124 and 64; the pulse rate was 132. She was markedly emaciated and very weak, with quadriceps loss, graded 3. Diffuse pigmentation of the skin was rather marked. Symmetrical enlargement of the thyroid gland, tremor of the fingers, exophthalmos and a positive Stellwag sign were noted. Cardiac enlargement was graded 2. A systolic apical murmur, auricular fibrillation and evidence of congestive heart failure as indicated by pretibial edema, moisture at the bases of the lungs and hepatic engorgement were also noted. On admission to the hospital the basal metabolic rate was +53.

The patient was treated on the medical service in the hospital for a period of twenty-four days during which time she received thirty drops of compound solution of iodin daily. The basal metabolic determination at this time was +41. During the course of examination a routine roentgenogram of the chest was made which exhibited areas of apparent destruction in the ribs posteriorly on both sides believed to be metastatic in origin (Fig. 246); healed lesions of pulmonary tuberculosis of both upper lobes and cardiac enlargement, graded 2, were reported. Roentgenograms of the spine and pelvis showed slight arthritis and bone atrophy. The hemoglobin was 78 per cent, erythrocytes numbered 4,240,000 and leukocytes, 5,200. A differential count was without incident save for lymphocytosis of 31 per cent. A nonprotein nitrogen determination of the blood was 30 mg. and serum bilirubin was 1 mg. (indirect van den Bergh reaction) for each 100 c.c. The blood Wassermann reaction and the urinalysis were negative. In view of the roentgenologic report on the chest, a careful search was made for a primary malignant neoplasm, but none was found unless the thyroid gland could be considered to have undergone malignant degeneration. A tentative diagnosis was made of severe exophthalmic goiter, probably undergoing malignant degeneration, and myocardial degeneration with auricular fibrillation and cardiac decompensation. December 15, tissue was removed from both lobes

of the thyroid gland for biopsy. The pathologist reported marked parenchymatous hypertrophy. December 24, after twenty-four days of medical preparation, subtotal thyroidectomy was performed. Again the pathologist reported marked parenchymatous hypertrophy. The patient died three hours after operation as a result of hyperthyroidism.

Postmortem examination did not reveal evidence of malignancy, either of the thyroid gland or elsewhere in the body. A healed lesion of pulmonary tuberculosis, marked atrophy of the liver, and pronounced generalized osteoporosis, especially of the ribs and skull, were found. The ribs were very friable. The calvarium was found to be extremely thin and was almost

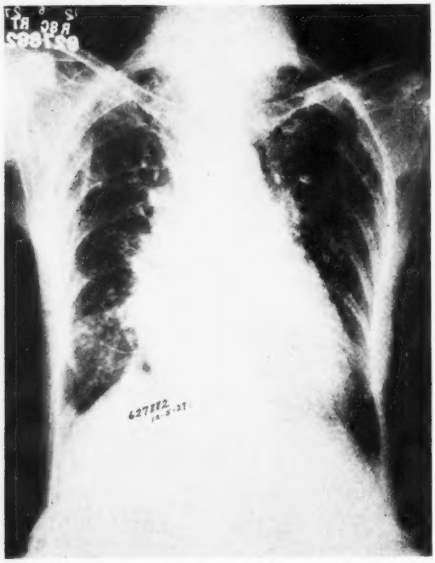

Fig. 246.—(Case 3.) Extreme porosity of the ribs, simulating metastasis.

translucent when held up to the light. The bone of the calvarium and ribs could be easily crushed between the fingers.

Case 4.—A woman aged sixty-four years registered at the clinic March 15, 1928. Gastro-enterostomy had been performed elsewhere in 1920, for some obscure gastric disorder. A goiter had appeared thirty years previously and had been increasing in size. Symptoms had been noted only in the last two and a half years. During this time she had lost weight and strength, had palpitation, tachycardia, dyspnea, hyperidrosis, and tremor, and was nervous. Toxic goiter had been diagnosed elsewhere eighteen months previously. She had been given compound solution of iodin and radium treatment, with some improvement.

On examination the weight was 93 pounds, which was 40 pounds below the usual normal weight. The blood pressure was 152 and 75; the pulse rate was 100. Adenomatous goiter with the usual clinical signs of hyperthyroidism was noted. The hemoglobin was 67 per cent, erythrocytes numbered 3,800,000, and leukocytes on two occasions numbered 4,600 and 6,900. The differential count was normal. A fractional gastric analysis disclosed total acidity of 10, free hydrochloric acid, 0, and a total quantity of 75 c.c. The basal metabolic rate was +45. The blood Wassermann reaction and urinalysis were negative. A roentgenogram of the chest showed marked

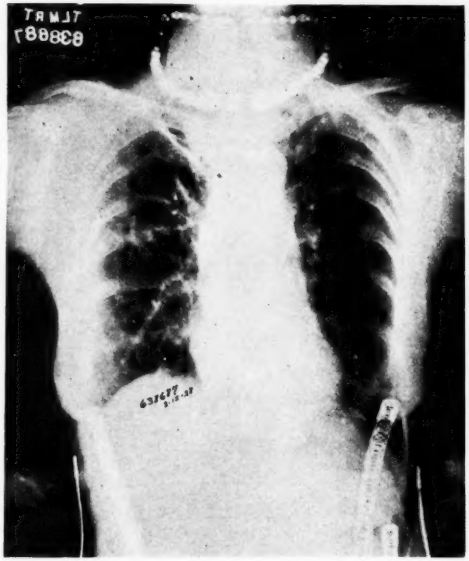

Fig. 247.—(Case 4.) Marked porosis of ribs posteriorly, especially on the left.

porosis of the ribs and again malignant disease was suspected (Fig. 247). Operation had been performed elsewhere for supposed carcinoma of the stomach, but the fluoroscopic examination at the clinic showed that gastroenterostomy had been performed, and it was therefore assumed that the lesion had been benign. Examination of the colon with the barium enema was negative other than the observation of a diverticulum of the sigmoid. Evidence of malignant disease was not found anywhere in the body, and in view of our experience in Case 3, it was suspected that the changes were secondary to the hyperthyroidism. Further study of the long bones revealed definite decalcification in the forearm and hand as compared with those of the control subject. A blood calcium determination was 10.2 mg. and inorganic blood phosphorus was 4.5 gm. for each 100 c.c. The final diagnosis was

adenomatous goiter with hyperthyroidism and secondary osteoporosis. April 4, 1928 subtotal thyroidectomy was carried out. The pathologist reported multiple hemorrhagic degenerating cystic adenomas. Convalescence was uneventful.

Case 5.—A woman aged fifty-four years registered at the clinic April 8, 1927. She gave a history of uncomplicated pneumonia, influenza and malaria. For the last four years she had noted weakness, loss of weight, palpitation, tachycardia, dyspnea, hyperidrosis, insomnia, intolerance of heat and exophthalmos.

Fig. 248.—(Case 5.) Very marked porosis of tibia and fibula.

When the patient came to the clinic she was bedridden because of so-called arthritis. The weight was 103, which was 30 pounds below the usual normal weight. The blood pressure was 146 and 84; the pulse rate was 134. A small, symmetrically enlarged thyroid gland with exophthalmos, graded 2, and quadriceps loss, graded 4, was noted. Examination of the heart disclosed enlargement, graded 1, with normal rhythm and without evidence of edema. She was placed in the hospital immediately for further study and treatment. A diagnosis was made of severe exophthalmic goiter. Basal metabolic determinations on four occasions were +33, +30, +27, and +33.

The urinalysis showed albuminuria, graded 1, and pyuria, graded 1. The hemoglobin on three occasions was 65, 75, and 85 per cent; erythrocytes numbered 4,000,000, 4,360,000, and 4,480,000 and the leukocytes 4,300, 5,600, and 7,200. The differential count was normal, other than lymphocytosis of 35 and 44 per cent on two occasions. The blood Wassermann reaction was negative. Roentgenograms showed generalized osteoporosis, especially of the femur and tibia (Fig. 248). There was pronounced porosis of the bones but the ribs did not show the marked change evident in Cases 3 and 4. After thirty-four days of medical care consisting of the administration of compound solution of iodin in doses of 30 to 50 drops daily, subtotal thyroidectomy was performed. The pathologist reported hypertrophic parenchymatous thyroid gland. Recovery was uneventful.

A SMALL CARCINOMA OF THE STOMACH; SYPHILIS OF THE STOMACH; INGUINAL RADIATION OF PAIN IN GASTROJEJUNAL ULCER; ACUTE YELLOW ATROPHY POSSIBLY DUE TO POISONING BY ATOPHAN; JAUNDICE DUE TO STONE IN THE COMMON DUCT ASSOCIATED WITH CARCINOMA OF THE BREAST; HEMORRHAGIC TENDENCY IN JAUNDICE; THE ASSOCIATION OF GALLSTONES AND DUODENAL ULCER

CHARLES S. MCVICAR AND JAMES F. WEIR

A SMALL CARCINOMA OF THE STOMACH

A MAN aged fifty-two years registered October 5, 1923, stating that eight years before he had had a sudden onset of severe, nonradiating, midepigastric pain, which lasted four or five hours. The epigastrium was tender for about a week and since, for a period of eight years, there had been a more or less continuous burning pain in the epigastrium which was relieved by eating. The pain frequently wakened him at night. Five months previous to examination he was put on a diet of milk with powders and was relieved of pain. He reported a weight loss of 20 pounds over a period of fifteen months.

At the time of examination anemia was not present. A test-meal showed a total acidity of 88 and free hydrochloric acid of 70. Roentgenologic study of the stomach, October 8, did not show anything abnormal. This was repeated, October 10, and was again negative. The patient was kept under observation with frequent feedings and alkalies and because of the consistence of history and the persistent tender point, operation was advised.

At exploration, October 22, 1923 (Pemberton), a small ulcer was found on the lesser curvature of the stomach about 5 cm. above the pylorus. This was excised and pyloroplasty performed. Ulcer in the duodenum was not found. The excised portion of stomach measured 5 cm. in diameter and the ulcer was 1 cm. in diameter. On histologic examination it was shown to be carcinomatous.

The patient returned in February, 1926, reporting a short period of relief followed by recurrence of cramping, burning, and epigastric pain, coming on five or six hours after food and relieved by food or water. He had had some bitter eructations but had not vomited. His weight had remained stationary. Erythrocytes numbered 5,120,000. A test-meal showed total acids 60 and free hydrochloric acid 40. Roentgenologic study showed a niche on the

lesser curvature just above the incisura. This was interpreted as a recurrent ulcer, probably malignant. The patient was submitted to reoperation February 11, 1926 (Balfour), when partial gastrectomy was done. Exploration revealed an ulcer on the posterior wall of the stomach 8 cm. from the pylorus. There was no evidence of recurrence at the site of the former excision. The ulcer found at this time measured 2.5 by 2 cm. On histologic examination it was classified as carcinoma, graded 3.

This patient presented a long history of dyspepsia that could easily be confused with that produced by benign peptic ulcer. Anemia was not present. The free gastric acidity was high. The excised carcinomatous lesions were small. The pyloroplasty permitted direct inspection of the inside of the duodenum and excluded a duodenal ulcer. The resection of the stomach enabled the surgeon to examine the stomach from within and to exclude benign ulcer. In explanation of the symptoms there seem only two alternatives: a benign ulcer, which became carcinomatous was present on each occasion, or slow-growing carcinomatous ulcers were present. In either case at a time when it was reasonably certain that the lesions were malignant the patient reacted to treatment after the manner of patients who have benign ulcers, that is, the symptoms were relieved and almost completely abated by frequent feedings and alkalies. The generalization frequently quoted that night pain means duodenal ulcer is called in question, since night pain was mentioned as a feature in the complaint. In the same manner we must examine the generalization that intragastric lesions smaller than 24 mm. in diameter ("quarter dollar") are likely to be benign. If optimal results are to be attained in the surgical treatment of gastric carcinoma we must aim at diagnosis when the surface area of the lesion is less than 17 mm. in diameter ("a dime"). Although it is true that resected specimens of carcinoma of the stomach have been, as a rule, larger than 24 mm. in diameter, this fact should not be accepted as a comprehensive diagnostic guide. It is rather an expression of tardy diagnosis. Finally, it may be pointed out that the roentgenologist is hampered in estimating the size of a small intragastric lesion. Furthermore, his interpretation of the pathologic nature of the lesion must, like that of the internist, depend on supple-

mentary data. In our present state of knowledge such data are usually wanting when the lesion is small, but it is on a better interpretation of small intragastric lesions that our attention should be focused. If we content ourselves with the fact that the majority of small intragastric lesions are benign, we will surely overlook a disconcerting number of early carcinomas. The most important immediate problem in the management of intragastric lesions is the development of methods which will enable us to differentiate small lesions.

SYPHILIS OF THE STOMACH

A woman aged forty-two years registered June 13, 1928. The patient stated that two years previously she had begun to complain of belching of gas, cramping pains in the abdomen, failing appetite, and general ill feeling and she "dragged around" for about a year; she then seemed to recover and had remained in fair health until seven weeks before admission, when the same sort of abdominal discomfort recurred. Five weeks later she began to vomit; at first the vomitus was watery, and then food was brought up. Her weight had fluctuated in a peculiar way. Previous to the onset of distress, two years previously, she had had a voracious appetite for a time and had gained weight from 135 to 165 pounds in four months. During the one-year period of ill health, she had lost weight to 110 pounds; as she improved she gained weight to 120 pounds, and during the recent upset she again lost 10 pounds.

On examination the patient appeared moderately well nourished. There was a suggestion of a small nodular mass just to the right of the umbilicus. There was no anemia. Two fractional test-meals each showed anacidity. The roentgenologic report was "extensive carcinoma of the lower half of the stomach, apparently free and operable." The blood Wassermann reaction was strongly positive. There was a history of premarital exposure fifteen years previous to examination. In spite of the roentgenologic appearance of the lesion it was felt that we were probably dealing with a case of gastric syphilis and a therapeutic test was decided on. The patient received, over a four-week period, six intravenous injections of arsphenamin in conjunction with a corresponding amount of mercury. At the end of one month there was no appreciable change in her subjective complaint, and roentgenograms did not show change in the gastric lesion.

Operation was therefore decided on and was undertaken July 21, 1928 (Balfour) when the distal half of the stomach was resected. The resected portion of the stomach showed multiple shallow irregular connecting and isolated ulcers (the largest 2.5 cm., the smallest 1 mm. in diameter). Histologic examination did not show evidence of malignancy. A search for spirochetes in specially prepared sections was unsuccessful. The patient convalesced satisfactorily, and antisyphilitic treatment is being continued.

In a discussion of the differential diagnosis of gastric syphilis and carcinoma of the stomach, it is usual to contrast the percentage incidence of certain observations; for example, syphilis is more constantly associated with anacidity and less often with palpable tumor, but such information is at best only suggestive. There is usually marked loss of weight in each disease but here one circumstance may help, namely, that whereas the loss of weight of patients with carcinoma is usually progressive the weight of the patient with gastric syphilis may at first decline rapidly and then remain stationary for months. Thus one may often observe an emaciated patient with gastric syphilis whose clothing fits well because it has been adjusted to fit the change in weight. In the emaciation of carcinoma, the clothing is obviously too large for the shrunken figure. The Wassermann reaction on the blood is of first importance, but it must not be forgotten that patients with carcinoma may also have a positive Wassermann reaction. In 535 consecutive cases of carcinoma of the stomach proved at operation, the Wassermann reaction was studied in 443 (82 per cent). In the group studied, nine patients (1.99 per cent) showed a positive reaction. The association, therefore, of roentgenologic evidence of an intragastric lesion and a positive Wassermann reaction is not a proof of syphilis of the stomach.

Fortunately there is one useful method of differentiation, namely, that the patient who has gastric syphilis will as a rule report prompt subjective improvement following the institution of specific treatment. Frequently this subjective improvement is associated with objective evidence in a gain in weight, and infrequently with a change in the roentgenologic appearance of the gastric lesion. The cases which are to be submitted to a therapeutic test may be divided into two groups: (1) Those in which the lesion would be frankly inoperable if malignant; one need have no hesitation in submitting this group to specific treatment, and (2) a smaller group in which the lesion is confined to the pyloric end of the stomach and is therefore accessible and resectable if it is carcinoma. The case reported here fell in the latter group and is remarkable in that there was failure to secure

subjective improvement under treatment. In view, however, of the extent of the area involved in ulceration, one is inclined to believe that there might have been impairment of motor function of the stomach under the most favorable response to antisyphilitic treatment.

INGUINAL RADIATION OF PAIN IN GASTROJEJUNAL ULCER

A man aged fifty-six years registered September 2, 1927. He gave a history of ten years of dyspepsia of the ulcer type previous to an operation done elsewhere in 1925. At the operation gastro-enterostomy was done and six weeks later the surgeon reopened the abdomen, not because any complication had ensued but to examine the lesion at the pylorus which at the first operation had the appearance of a neoplasm. At this time the induration had subsided and it was possible to locate an ulcer in the duodenum. Nothing else was done at this time on the stomach or duodenum but a right inguinal hernia was repaired. The patient remained free of symptoms for about seven months when he had a recurrence of epigastric pain similar in situation to the original discomfort, less severe and presenting the same food or soda ease. He next had twelve or more attacks of pain in the lower part of the abdomen, across the hypogastrium and radiating to each inguinal region. This discomfort was also relieved by food and soda, although less completely than the epigastric discomfort. Two weeks before registration he had vomited several liters of gastric content which looked like blood. There had been no gross hemorrhage before operation, and he had not observed tarry stools.

On admission the hemoglobin was 49 per cent. The gastric acids were: total 34 and free hydrochloric acid 22. The roentgenologic appearance of the stomach and stoma was indeterminate. The roentgenologist asked for another roentgenologic examination but the indication for operation seemed clear and the patient was submitted to operation with a diagnosis of gastrojejunal ulcer.

At operation, September 6, 1927 (Balfour), the gastro-enterostomy opening appeared to be free of obstruction and functioning well; there was slight induration along the posterior aspect. It was disconnected and a subacute ulcer, 1 cm. in diameter, was found on the posterior aspect, half of it on the gastric side and half in the jejunum. The anastomosis was excised with the ulcer. The openings in the stomach and jejunum were closed and gastroduodenostomy was performed.

As a rule the diagnosis of gastrojejunal ulcer is not difficult. Whereas the pain of the original ulcer is likely to be indicated by the patient pointing with the tips of the fingers to the epigastrium, that of a stomal ulcer is lower and to the left and is indicated by a sliding motion of the palm or ulnar edge of the hand. As pointed out by Carman, Moore, and Camp, all of the

roentgenologic signs of gastrojejunal ulcer except the niche or crater may be simulated by a nonulcerative deformity of the stoma. In the absence of a visualized crater a roentgenologic diagnosis of gastrojejunal ulcer must therefore be supported by the clinical history of dyspepsia having a daily ulcer sequence (food, ease, pain), and the pain must be felt in a new situation. If in the presence of roentgenologically visible deformity at the stoma there is recurrence of the discomfort in the same area as before operation, it is safer to assume that there is reactivation of the original ulcer due to malfunction of the gastro-enterostomy opening. Infrequently in such a case there may be a stomal ulcer, with mild symptoms masked by the more impressive original ulcer. But it is in the occasional case in which roentgenologic evidence of a gastrojejunal ulcer is lacking that symptoms become important. In the case described there was inguinal radiation of pain. This evidence for stomal ulcer is in our experience conclusive. The interpretation of the inguinal radiation has been an inviting problem. One plausible explanation was that gastrojejunal ulcers usually show perforating tendencies and are as a rule adherent to the colon or mesocolon and because of this show a lower segmental distribution of pain. But since in this case the stoma was quite innocent of such involvement the explanation fails and since it fails in this characteristic instance it is probably not the correct explanation in any case. In this case the coincidence of a recurrent right inguinal hernia might have been assumed as a possible cause of the inguinal radiation of pain, but the pain disappeared after surgical treatment of the gastrojejunal ulcer and in spite of the persistence of the hernia.

ACUTE YELLOW ATROPHY, POSSIBLY DUE TO POISONING BY ATOPHAN

A woman aged thirty-seven years registered April 19, 1928, with the complaint of jaundice. She stated that she had been reasonably well until she had influenza during the epidemic of 1919. Since then she had not felt strong. She married at the age of thirty-four and had one child aged twelve months. During pregnancy there had been some emesis but the condition of the urine had been carefully followed and it had been consistently normal. Following normal delivery she had failed to gain strength, but had attributed

this to broken rest necessitated by caring for the baby. There had been some general aching for which she had taken various analgesics, especially pyramidon and atophan. Four weeks before admission she had a digestive upset with nausea, but without vomiting. She next noted generalized pruritus. Two weeks after the itching commenced, she became jaundiced. Two days before admission there had been some epigastric pain which was associated with bilateral high lumbar pain.

On admission the serum bilirubin was 6 mg. for each 100 c.c. The jaundice cleared rapidly and duodenal drainage showed that bile was reaching the intestine freely. April 20, 1928, a cholecystogram showed an apparently normal gallbladder. The diagnosis was not clear. The course suggested intrahepatic disharmony, but the transverse back pain suggested pancreatic involvement. The patient was dismissed April 26, 1928, and returned July 10, 1928 with recurrence of jaundice. She had remained well about eight weeks; then one night she had a digestive upset with nausea and vomiting. There was no pain at this time except slight aching in the epigastrium. Two days after this digestive upset, jaundice appeared. Pruritus followed the jaundice but was not so troublesome as in the previous attack. On this admission the jaundice was very deep, the serum bilirubin measuring 30 mg. for each 100 c.c. There was a slight tinge of bile in duodenal siphonage. The course of the illness following this admission was progressively unfavorable, prostration was marked and there was constant nausea and anorexia. An erythematous eruption and abdominal distention developed and the patient became delirious. The serum bilirubin fluctuated between 30 and 39 mg. over a ten-day period and then showed a rather marked drop to 20 mg. before death, July 29. During the fulminating period of the illness, there was no evidence of enlargement of the spleen. Persistent abdominal distention made it difficult to be sure of any decrease in the size of the liver. It was not possible to demonstrate leucin or tyrosin crystals in the urine. The urinary output was adequate. There was no significant change in the blood urea, blood sugar, or carbon dioxid combining power of the plasma.

At necropsy the liver presented the gross and histologic evidences of acute yellow atrophy. The organ weighed 1,045 gm. There was no evidence of disease in the gallbladder, ducts or pancreas.

Painless jaundice associated with a free or fairly free flow of bile into the duodenum, and a steadily declining serum pigment curve is strong presumptive evidence of intrahepatic disharmony, and enables the classification of a case as nonsurgical. There was a little element of doubt caused by the presence of some pain across the upper lumbar region. During the progressively unfavorable course of this patient's illness following the second admission, there was a good deal of epigastric discomfort, enough to cause reconsideration of the possibility of obstruction to the biliary ducts in spite of the previous negative cholecysto-

gram. It has been observed that a number of patients who have jaundice classified under the term "intrahepatic," have what they refer to as rheumatic pains as initial phenomena. Many of them report the use of salicylates, and a few have used atophan. In this instance the patient had used an undetermined amount of atophan during a year of debility following the birth of her child. She had also slight evidence of toxemia during pregnancy and whether either or both of these known possibilities had initiated the degenerative changes in the liver could not be shown, but the case serves to call attention to the increasing number of case reports illustrating the possible toxic action of atophan on the liver. It also calls attention to the fact that cases of intrahepatic jaundice, whether classified as infectious, toxic or catarrhal, may occasionally pursue an unfavorable course, and terminate in acute atrophy. Leucin or tyrosin crystals were not recovered in the urine of this patient although they were consistently sought. There seem to be no consistently infallible signs or laboratory criteria in acute atrophy of the liver. Perhaps the most suggestive information is conveyed by the clinical appearance of fulminating toxemia in a deeply jaundiced patient.

JAUNDICE DUE TO STONE IN THE COMMON DUCT, ASSOCIATED WITH CARCINOMA OF THE RIGHT BREAST

A woman aged forty-nine years registered November 20, 1928, with a complaint of jaundice of four weeks' duration. She had had four attacks of indigestion, one in February, one in May, one in September, and one in October; these attacks were characterized by slight epigastric discomfort, nausea, regurgitation and, on two occasions, vomiting. Actual colic had not been present, and she was improved after a night's rest. Following the fourth attack she became jaundiced and the icterus persisted until she came to the clinic. She had not had chills or fever.

Examination showed the patient to be slightly anemic; the erythrocytes numbered 3,850,000. There was leukocytosis on admission, the leukocyte count being 20,000. There had not been loss of weight. There was a nodule about 3.75 cm. in diameter in the right breast. The skin over this area was not adherent and the mass was freely movable. The stools did not contain bile. The patient was placed under observation in hospital and duodenal siphonage was planned. On passing the duodenal tube, gastric retention was encountered and on lavage of the stomach, food taken more than twenty-four hours before was recovered. Roentgenologic examination was then made of the stomach which showed this organ to be normal, but a deformity was found

in the second portion of the duodenum, which had the appearance of a large diverticulum. During the succeeding week, duodenal drainage was attempted on three other occasions, without obtaining any bile. The fourth siphonage was, however, rewarded by a very free flow, 210 c.c. of dark amber-colored bile being recovered. Roentgenologic study of the duodenum was repeated and this again showed what appeared to be a diverticulum in the duodenum, directed mesially and commencing, apparently, about 10 cm. from the pylorus. The serum bilirubin readings are shown in Figure 249. December 1, the patient had her fifth bilious attack with nausea and epigastric discomfort, but no actual pain. Following this the serum bilirubin had risen to 17.6 mg.

December 17, 1928, the right breast was amputated (Judd) and the mass proved to be a carcinoma, 2.5 cm. in diameter. Four days later exploration (Judd) revealed a completely destroyed gallbladder with a markedly

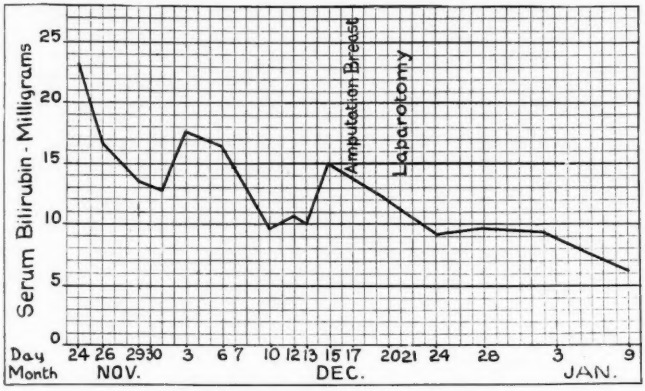

Fig. 249.—Serum bilirubin readings.

dilated common duct, which contained one large round stone. The deformity in the duodenum was produced by adhesions to the site of the necrosed gallbladder. The liver was hard and granular. The stone was removed from the common duct and drainage was instituted by means of a T-tube.

Although operation was advised after a short period of observation, this patient wished to postpone it and advantage was taken of this to continue our observations. The case is perhaps an instance of the so-called "silent" stone in the common duct. At any rate, colic was not present. There were, however, five episodes of distress sufficiently impressive to be clearly dated. The patient was phlegmatic in temperament and her threshold for pain was perhaps unusually high. This

seems probable since she was unable to recall an illness which might have coincided with the severe inflammation which had caused destruction of the gallbladder and distortion of the duodenum.

The significant features leading to a diagnosis of nonmalignant obstruction of the common duct were: The free flow of bile obtained on the fourth siphonage of duodenal contents, and the temporary rise in the declining serum pigment curve following the fifth "bilious" upset. The serum pigment curve is sustained or rises when jaundice is due to compression of the common duct by a neoplasm. Exceptionally there may be a slight decline if there is associated hemorrhage. The serum bilirubin then declines proportionately with the hemoglobin and from the same cause: dilution of the blood from leakage of pigment. There was always before us the roentgenogram suggesting a diverticulum of the duodenum. The apparent diverticulum was directed mesially and it would be difficult to imagine a hollow diverticulum exerting sufficient pressure on the duct to cause obstruction. After the malignant nodule in the breast was found, we were forced to review the evidence for benign obstruction of the common bile duct. If we were to assume the jaundice due to malignant metastasis it would not be remedied by surgical procedures. In jaundice due to metastatic infiltration of the liver there is usually free flow of bile into the intestine; if due to a metastatic lymph node compressing the common duct, there would not have been relaxation. Finally it must be acknowledged that the case presents a combination of pathologic observations so rare that generalizations permitting exact diagnosis cannot be elaborated. The point to be decided was whether the jaundice was likely to be relieved by surgical procedures. The evidence pointed to intermittent obstruction of the common duct, and intermittent obstruction is characteristically due to benign causes.

HEMORRHAGIC TENDENCY IN JAUNDICE

A man aged fifty-five years registered November 19, 1928, with a complaint of jaundice. He had undergone operation elsewhere in February, 1928, when the gallbladder, which contained stones, was removed. Bile

drained from the incision for five weeks. The wound then closed and he remained well for four months. About September 1, jaundice appeared and persisted with perhaps some fluctuation in intensity.

On admission the serum bilirubin measured 8.6 mg. for each 100 c.c. There was a scanty flow of bile on duodenal drainage on two occasions and bile was not recovered on three other occasions. A diagnosis was made of partial stricture of the common bile duct. The coagulation time, by the Lee and White method, varied on repeated examinations between ten and twelve minutes, and was not influenced by the intravenous injection of calcium chlorid in doses of 0.5 gm. on three successive days. Although the coagulation time was not markedly prolonged it was not considered completely satisfactory and on November 28, 700 c.c. of 6 per cent solution of gum acacia in physiologic solution of sodium chlorid was given intravenously. The patient had a rather sharp reaction in this procedure, becoming chilly and faint; then he began to sweat and one hour later had widespread urticaria. There was no rise of temperature. This reaction was similar to that occasionally encountered after blood transfusion. The blood coagulation time dropped from nine to five minutes during the next six hours, but on the following day it had regained the former height of ten minutes.

Operation was undertaken November 30, 1928, when a stricture of the common duct was opened and reconstruction was carried out over a T-tube. Three weeks later the patient was free from jaundice. There was then a normal quantity of serum bilirubin, which, however, still gave a direct reaction. There was no postoperative hemorrhage or oozing.

The coagulation of blood in vitro is accelerated by contact with any one of a multitude of substances. It is probable that many substances would enhance the clotting power of blood if injected in vivo. In this case, gum acacia solution was used with apparent success. It will be observed, however, that the injection of the solution was followed by an urticarial eruption and signs of mild anaphylactic phenomena, and the question arises as to whether the reduction in coagulation time was due to the direct action on the blood of the added colloidal solution or to a general systemic reaction induced by its injection.

THE ASSOCIATION OF GALLSTONES AND DUODENAL ULCER

A farmer aged sixty years had had periods of abdominal distress for thirty years. He had pain in the right upper quadrant and right lower quadrant with nausea and vomiting. The daily discomfort during spells was most apparent about 4 p.m. and 10 p.m. Supper taken at 6 p.m. did

not give relief. Vomiting, belching or soda gave temporary ease. Jarring, as in riding on farm implements, aggravated the discomfort. The appendix had been removed sixteen years previously without influence on the character or frequency of the discomfort. In the last three weeks the distress has been more insistent and five hypodermic injections of opiates have been required to relieve pain in the right upper quadrant which radiated straight through to the right lumbar region.

A fractional test-meal showed readings of free acid as follows: 0, 40, 36, and 10. A cholecystogram showed a poorly functioning gallbladder with stones. Roentgenologic studies of the stomach and colon were negative. A note was made of the ulcer features in the history, but the patient was submitted to operation with a diagnosis of cholecystitis with stones.

At operation, August 28, 1928 (Walters), there was a subacute perforating duodenal ulcer on the anterior wall of the duodenum and about 1.5 cm. below the pylorus. This was adherent to the pancreas. The gallbladder contained a single stone which was not faceted, 1.5 cm. in diameter. The stone was removed and the gallbladder was drained. Posterior gastro-enterostomy was done.

The possible association of gallstones and duodenal ulcer is of interest not only in diagnosis but also because the proximity of the gallbladder and duodenum has been assumed to subject them to common pathogenic agencies. In an attempt to learn something of the frequency of coincident disease we examined the histories of 500 consecutive cases of duodenal ulcer, proved by operation, and of 500 consecutive cases of gallstones treated by operation.

The tabulation shows the sex incidence in cases treated surgically, and also illustrates the possible confusion that may arise from statistical studies. Obviously either analysis might be quoted as indicating the coincidence of the two diseases. In one instance it would appear that the coincidence of duodenal ulcer and gallstones in males was 10 per cent, and in the other instance less than 2 per cent. If, however, the two groups are added, the conditions are found to be coincident in forty-one of the 1,000 patients, in twenty-two (3.9 per cent) of the 558 males and in nineteen (4.3 per cent) of the 442 females. In a more comprehensive study (4,679 cases proved at operation) Eusterman found that 4.63 per cent of all of the patients had gallstones, and 3.94 per cent had disease of the gallbladder without stones. This association is of importance in differential diagnosis, but is

TABULATION

SEX INCIDENCE IN CASES TREATED SURGICALLY

Operation for:	Cases.	Males.	Females.	Females.				Males.			
				With duodenal ulcer.		With gallstones.		With duodenal ulcer.		With gallstones.	
				Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Gallstones.....	500	140	360	13	3.61			14	10		
Duodenal ulcer....	500	418	82			6	7.3			8	1.9

relatively too infrequent to support a thesis that the two diseases are due to a common etiologic agent. In fact it is probable that the incidence of cholecystic disease in the ulcer group is not much greater than that of any comparable age group of the general population, and conversely that the incidence of duodenal ulcer in patients who have cholecystic disease is not greater than the incidence in those of comparable age who have normal gallbladders.

RECOVERY FROM VALVULAR LESIONS IN CHILDREN

SAMUEL AMBERG AND FREDRICK A. WILLIUS

IT seems to be generally accepted among physicians that valvular diseases of the heart never heal completely. Nevertheless, evidence has been brought forward to show that such full restitution to the norm has occurred, and that complete recovery is not rare. Since our literature is rather silent on this subject it may be permissible to cite a few illustrative cases from the literature and to add a few observations of our own.

Leyden, in 1889, after reviewing a number of cases, reached the conclusion that not only murmurs, but all cardiac symptoms disappear. His cardinal requirement is the lasting disappearance of murmurs. He stated that unquestionable mitral and aortic lesions disappeared completely in the course of time, although the latter more rarely.

A footnote by Zenker in a paper of Ebstein contains a report of a case of a boy, aged twelve years, who in the course of chorea and acute articular rheumatism acquired severe endocarditis, leading to embolic manifestations. The boy recovered, but a mitral systolic murmur persisted for several years. In the course of time the murmur disappeared entirely; the patient did not have further cardiac symptoms, and led the life of a healthy robust farmer.

Aufrecht observed two boys, one five years of age, the other twelve. Following acute articular rheumatism both had loud systolic mitral murmurs, with enlargement of the heart, for several months. A year later all evidence of the cardiac lesion had disappeared and this recovery could be followed in one case to the forty-fifth year of life, in the other, to the fiftieth year.

In two cases, reported by Friedlander, a diastolic murmur of aortic insufficiency with a mitral murmur existed in girls ten and thirteen years of age, who had pericarditis. This diastolic murmur disappeared in ten to eighteen days. In the latter case the lesion presumably occurred in the course of pneumonia; in the former, it followed acute articular rheumatism.

The frequency with which recovery, as indicated by the disappearance of murmurs and absence of cardiac symptoms, occurs in children cannot yet be expressed in reliable figures. Of 250 patients with acute endocarditis studied by Ledford, only two left the hospital without murmurs. Scherer, in accord with other writers, was convinced that he had often noted recovery from mitral endocarditis. He emphasized the possibility of complete recovery, especially of the slight mitral insufficiency of childhood. John and Nobel estimated that complete cure occurs in about 26 per cent of rheumatic cardiac lesions in childhood. Poynton cited data furnished him by Thompson, that of eighty-three patients examined repeatedly, twenty-four who were admitted with the diagnosis of carditis later were found to have normal hearts. Coombs placed cases of cardiac rheumatism in two groups, the first of which included cases with signs so slight as to make the initial diagnosis uncertain, and the other, only those in which the diagnosis was definite. Of 300 cases of the first group physical signs of the cardiac disease were lost in 115 and of 200 cases in the second group, all physical signs of the disease were lost in about fifty.

According to Coombs: "But a majority of those patients who have lost such signs as they did present, belong to a very definite category. A child comes up to be treated for some articular pain, or a moderate attack of chorea, and a small increase in the area of dulness is noted, with displacement of the point of maximal impulse to the left, and a definite systolic murmur centering upon that point. Some of the patients have already lost their sign of cardiac disease by the end of the illness that brought them under observation while in others the signs disappear more gradually."

Such data seem to offer some subjective latitude in inter-

pretation. We do not wish to enter into a discussion of the permissible variations in the area of the cardiac dulness in children and the situation of the maximal apical impulse, which may be outside of the mammillary line. If the cardiac dulness and the point of maximal systolic impulse fall outside the nipple line during early childhood, their recession to within the nipple line in late childhood cannot be accepted as evidence of previous enlargement. It may suffice to state that better standards are desirable. An apical systolic murmur not transmitted to the axilla and disappearing with the acute illness is also of questionable significance with regard to endocarditis.

Although the frequency with which acute endocarditis may disappear completely is still in doubt, it is certain that such recovery can take place. If more than one valve is injured, the evidence of the lesion of only one valve may disappear. Such occurrences may be illustrated by the following two cases.

A boy aged ten years had acute articular rheumatism, followed by mitral endocarditis, with enlargement of the heart, transmitted systolic murmur and a strongly accentuated secondary pulmonic sound. Shortly afterward a diastolic aortic murmur was established. After a period of about a year the diastolic murmur gradually became less distinct until it could no longer be detected. The mitral murmur persisted, with the addition of a questionable presystolic murmur.

Here, as in the cases of Friedlander, a diastolic aortic murmur which had persisted for some time disappeared completely. Cabot and Locke have pointed out that diastolic murmurs suggesting aortic lesion may occur, without showing valvular lesions at necropsy. Furthermore, Morse reported that under certain conditions, such as profound anemia, a diastolic aortic murmur may be heard in children. We observed a case of Adler's, which was later reported by him, in which such a murmur disappeared promptly on transfusion. Friedlander concluded that in his cases any other explanation for murmur, than that of aortic valvular disease, would be too forced, although both of his patients had pericarditis. We believe that the persistence of the aortic murmur for a long period of time, as in the case of

our patient who was in excellent condition, makes it justifiable to consider it as due to aortic valvular disease. It will be difficult to prove, clinically and anatomically, the healing of a valvular lesion.

The second case was that of a girl aged eight years with chorea who was admitted to the clinic suffering from subacute rheumatic mitral endocarditis; later pericarditis occurred. About two months after admission clinical signs of aortic insufficiency became manifest. Shortly after the removal of severely infected tonsils much general improvement occurred and the patient was taken home, to be kept absolutely at rest. On her return to the clinic after six months, the systolic mitral murmur had disappeared but the evidence of the aortic lesion remained.

More striking is the case of a boy aged six years, who, one year preceding admission to the clinic, had had an illness in which a high fever lasted three days. Two weeks later the physician had found a cardiac complication. At the time of the child's admission to the clinic, the heart was enlarged and a systolic murmur was present, with the maximal point over the apex, transmitted to the axilla. The second pulmonic sound became accentuated after several days of complete rest. He was sent home for complete rest and returned after six months, at which time the cardiac dulness was found to extend 7 cm. from the median line to the left, instead of 9.5 cm., as it had been on his first visit. Only on exercise could a faint systolic murmur be made out over the apex, and two successive examinations, one four and the other eight months later, disclosed a normal heart without enlargement and without murmurs. The child was also in good general condition.

In this case, all evidence of a clinically unquestionable mitral endocarditis disappeared within a period of one year from the time the boy was first seen and within two years from the time of its probable appearance.

Another case is that of a girl, aged nine years, who entered the clinic in January, 1923, for treatment of bilateral otitis media suppurativa. At that time the heart was normal. In

May, 1924, she returned to the clinic suffering from acute endocarditis and enlarged heart. The dulness extended 13 cm. from left to right with the point of maximal impulse well outside the nipple line; an apical systolic murmur was transmitted to the axilla; the second pulmonic sound was accentuated. In November of the same year, the child was brought to the clinic with acute appendicitis. The heart was still enlarged and the murmur persisted. After appendectomy she was kept at complete rest. In February of the following year, the dulness of the left side of the heart was just outside the nipple line; the point of maximal impulse was just inside. The dulness at the right reached the sternum; a soft systolic murmur at the apex was transmitted to the axilla. In September, enlargement of the heart could not be made out and the murmur had completely disappeared. The child was in good condition and attended school. Another examination at the end of the year showed the heart to be normal.

Two other cases of complete disappearance of a systolic apical murmur, well transmitted, were observed, but the lesions were not as sharply defined as in the previous case.

The first of these two cases was that of a girl, aged seven years, taken ill with acute osteomyelitis and staphylococcus septicemia with local outcroppings, and involvement of the pleura, lungs, genito-urinary tract, and pericardium, which necessitated pericardiotomy with removal of thick fibrous exudate. After a period in hospital the girl recovered with the exception of a few remaining fistulas on the lower extremities, and at no time could a lesion of the heart or pericardium be discovered. Two years after the onset of the osteomyelitis, chorea developed following the removal of acutely infected tonsils, and in the course of the chorea there occurred an apical systolic murmur transmitted to the axilla, its area mainly outside the nipple line. Definite cardiac enlargement was not present. Two weeks after admission to the hospital the systolic murmur disappeared, and two weeks later all evidence of chorea had disappeared. The temperature during most of this period had been elevated, rarely exceeding 101° F. The systolic

murmur did not return during an observation period of two years; the heart was normal.

The second case was that of a girl, aged eleven years, brought to the clinic because of recurring chorea. Mitral endocarditis and moderate secondary anemia also were found. The chorea was not severe, but yielded slowly. There was a definite systolic apical murmur well transmitted to the axilla. The enlargement of the heart on percussion was questionable, but repeated roentgenograms showed moderate enlargement. This remained unchanged, although the systolic murmur disappeared entirely, even when the patient began to get up and move about, which she did shortly before leaving for home.

COMMENT

In the first of the two latter cases definite enlargement of the heart was not present, and in the second there was moderate enlargement which persisted, although the murmur disappeared. Also, the time of observation was too short and for these reasons we cannot speak of complete recovery in these cases. The electrocardiograms did not show anything that was noteworthy in any of our cases.

It would seem safer, for the time being, to speak of a completely healed case of endocarditis as one in which the signs of a valvular lesion had been clearly established and had persisted for some time. Mitral murmurs which are not transmitted to the axilla, and which cease with the cessation of a febrile disease of rather short duration can hardly be accepted as evidence of valvular disease. The diagnosis of slight degrees of cardiac enlargement during childhood is often difficult.

In order to avert misunderstanding, we wish to state clearly that the disappearance of all signs of cardiac involvement, with complete healing of the lesion, does not imply that the heart anatomically would not disclose residual evidence of disease of the valve leaflets, ring, or mural endocardium. It is not an uncommon observation in adults that minimal residual endocardial lesions are demonstrable at necropsy when cardiac symptoms had not been present during life and when object-

ive signs of heart disease were not disclosed on careful examination.

We adhere to prolonged complete rest as the treatment for cases of cardiac disease. Not only in the cases mentioned, but in others, it has given satisfactory results.

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THE VALUE OF TREATMENT BY MALARIA IN NEUROSYPHILIS; ILLUSTRATIVE CASES

PAUL A. O'LEARY

TREATMENT by malaria in cases of parenchymatous neurosyphilis, as originally suggested by Wagner von Jauregg, has proved to be the outstanding recent advance in the treatment of neurosyphilis. A review of American and foreign literature shows that in approximately 30 per cent of cases in which there are clinical signs of general paresis remission develops following the fever course. Of the fifty-seven patients with early clinical signs of general paresis, whom I treated during 1924, 41 per cent are still in remission. The fact that the percentage of remissions obtained in this group is slightly higher than those reported in the literature is probably due to the fact that my patients showed early clinical signs of paresis. The clinical evidence in some of the cases did not warrant a diagnosis of frank paresis at the time the treatment by malaria was instituted, but in view of the fact that these patients had been under my care for several years, had received intensive treatment of several varieties, had continued to maintain persistently positive serologic reactions of spinal fluid and blood, in addition to presenting presumptive symptoms of early mental changes, the diagnosis of early general paresis was made. A separation from this group was made of those cases in which reactions of spinal fluid and blood remained persistently positive, and in which the colloidal benzoin and colloidal gold reactions were of the paretic type (zone I) but without signs of mental degeneration. These cases were classified as paresis sine paresi or asymptomatic paresis.

The basis for appraising clinical remissions I believe is pertinent. In my work the economic status of the patient, following

the treatment by malaria, was the criterion which determined whether or not a remission had developed. In the cases that presented sufficient clinical evidence to warrant a clinical diagnosis of paresis such an appraisal was not difficult, whereas in the cases of the early type longer observation periods were necessary before deductions were attempted. Significance was not attached to changes in the objective signs of the disease after the treatment as it was anticipating too much to expect regeneration in the central nervous system even though the somatic symptoms were materially improved. Neither was significance attached to the status of the spinal fluid nor to serologic reactions of the blood, for the first two years following the course of treatment by malaria. However, continued observation of the spinal fluid and of serologic reactions of the blood has shown a reversal to negative in a high percentage of the cases in which clinical improvement also was shown. The following five cases are illustrative of the variety of results observed following treatment by malaria.

Case 1.—The patient was a middle-aged successful lawyer. During the winter of 1925 his business associates noted unusual extravagance and a decrease in the acuity of his judgment and decision. The extravagance was noted, particularly, in extensive and unwarranted real estate ventures, in addition to a hobby for the frequent purchasing of expensive automobiles. These changes progressed rather rapidly and in April, 1925 he had become so irritable, agitated, destructive, and threatening, that he was placed in an asylum. After a four months' sojourn there his condition was practically unchanged, and on admission to The Mayo Clinic, mild restraint was necessary. At this time the Wassermann reactions on the blood and spinal fluid were strongly positive, the Nonne reaction was positive, lymphocytes numbered 91, polymorphonuclear leukocytes 20, and the colloidal benzoin reaction was 002 320 333 333 000. In July the patient was inoculated with *Plasmodium vivax*. The course of the malaria was very stormy because of the extreme dementia but he nevertheless completed a series of twelve pyrexial paroxysms. The convalescence from the malaria was protracted, extending over a period of two months. During this time, however, the patient was docile and easily managed. He returned steadily to his former mental state and eight months after the course of malaria resumed his duties in his law office. Antisyphilitic treatment has not been given since the treatment by malaria three and a half years ago. He still is in a complete remission and has regained and maintained a successful law practice. In July, 1928 the reactions of spinal fluid and blood were completely negative in all factors and objective signs of paresis were not present.

This is an example of an ideal type of paresis to treat by malaria. Although the patient was acutely demented very little cerebral degeneration had occurred. Unfortunately it is often not possible to estimate the degree of degeneration and hence it is not always possible to prognosticate the result of the treatment by malaria. This case also presents a striking example of the value of the treatment, unaided by any other type of antisyphilitic medication, in producing complete remission. The clinical improvement is encouraging, and the reactions of the blood and the spinal fluid, which have been reversed to negative throughout, are particularly encouraging. The mechanism by which such results are accomplished is not understood. Neither is the status of antisyphilitic treatment after treatment by malaria understood. There have been many patients of this type who, following the course of fever, disappeared from observation for several years but who, when reëxamined, were found to be greatly improved both clinically and serologically. There have been others in whom the clinical and serologic improvement was negligible until they were placed on arsphenamin, tryparsamid, intraspinal measures, and mercury or bismuth.

Case 2.—This patient came to the clinic in May, 1924, from the local State Hospital, where he had been confined during the last four months. The first evidence of paresis was noted in his inability to carry out the orders of his employer, which necessitated his dismissal. He was very forgetful, was extremely syphilophobic, had a tremor about the mouth and slurring speech, and was unable to coöperate. Wassermann reaction of blood and spinal fluid were strongly positive. The Nonne reaction was positive and cells numbered 8, the colloidal benzoin reaction was 023 333 333 330 000. Another of the patient's chief complaints was excessive salivation and a sensation of burning in the mouth which, of course, annoyed him considerably. He received four courses of tryparsamid for a total of forty-one injections in conjunction with an equal number of intramuscular injections of bismuth. It was found necessary to discontinue the tryparsamid because of subjective and objective visual complaints. When the tryparsamid was discontinued, the spinal fluid was about the same and the patient's general condition was only slightly changed. He had gained 8 or 9 pounds but was unable to retain a position, ptyalism was still observed, and he was unable to get along with his family. Accordingly, he was inoculated with malaria in April, 1925; no other treatment was given. He was examined again at the end of a year following the course of treatment by malaria. The Wassermann reaction on the spinal fluid was practically unchanged. In the meantime, he had

returned to his former occupation which he has been able to maintain satisfactorily. Further treatment has not been given. Tests of the spinal fluid remain positive, and the patient is in a complete remission. His work does not entail much mental effort, and he has been carrying it on successfully for three years.

This case is not presented in an effort to compare treatment by malaria and treatment by tryparsamid but, particularly, to call attention to the marked improvement in the patient's subjective complaint which has not been accompanied by reversal of serologic reactions.

Tryparsamid is a valuable agent for the treatment of neurosyphilis and it supplies a definite niche in the armamentarium of the syphilologist. It may be given to the patient with neurosyphilis who is somewhat debilitated from syphilis or from some other condition, or to one whose general condition does not warrant an intensive fever course. In my experience it has also been of definite value as an adjunct after treatment by malaria. The advisability of giving a large series of injections (seventy or more) entails a time element that must be considered.

The rapidity with which remissions develop following the treatment by malaria is frequently astounding. A complete reversal of personality, wherein a docile, unassuming character will supplant the former rabid, egotistic type is common. On the other hand, I have often seen a spirit of self-assertion develop in a patient who previous to the treatment was leading a humdrum, almost vegetative, existence. These character changes develop early and are often the outstanding result of the treatment by malaria because they permit of such marked contrasts. The amount or type of medication given previous to the course of malaria does not seem to influence the results in a comparable group of cases, although there has been a higher percentage of remissions in the group in which previous treatment had not been given than in the group in which treatment had been given over a long period. This variation is due to the fact that in the latter group the parenchymatous changes are more advanced and complete remissions are hence less frequently noted.

Case 3.—The patient came to the clinic in August, 1923, and the diagnosis of paresis sine paresi was made, because of the positive Wassermann reactions of the blood and spinal fluid, positive Nonne reaction, 19 cells, and colloidal benzoin reaction of 333 333 333 331 000. Neurosyphilis had been recognized about five years previously and the patient received intensive treatment consisting of more than 100 injections of arsphenamin with a corresponding amount of mercury. Symptoms suggestive of paresis had not been present at the time of examination and the neurologic data were not sufficient to warrant a diagnosis of parenchymatous neurosyphilis. In view of the persistence of the positive Wassermann reaction of the spinal fluid and the intensive arsphenaminization, the patient was inoculated with *Plasmodium vivax* in October, 1924. The course was uneventful and he did not receive antisyphilitic treatment afterward. At the end of the first year following the treatment by malaria there was practically no change in the spinal fluid. At the end of the second year, the Wassermann reaction was weakly positive and the cell count had decreased to 3; there was an atypical colloidal benzoin curve. Three years after the course of malaria the reactions of the spinal fluid and blood had reverted to negative in all factors and the colloidal benzoin curve was of the syphilitic or tabetic type. The patient gained 22 pounds and has had none of the subjective symptoms he complained of previous to the course of malaria.

This report demonstrates the most ideal type of case for treatment by malaria. If a patient has been intensively treated with the various arsenical preparations or its modifications, over a period of years, and the spinal fluid maintains characteristics suggestive of paresis, my experience warrants the assertion that this patient is a candidate for treatment by malaria. The patient whose spinal fluid relapses chronically belongs in the same category because the tendency for the reactions of the spinal fluid to reverse repeatedly to positive when treatment is discontinued suggests an unfavorable outcome. I do not mean by this that every patient with asymptomatic neurosyphilis is a potential candidate for treatment by malaria, because a high percentage of these patients will manifest satisfactory and permanent serologic reactions from the accepted application of arsphenamin, mercury, and so forth, and if frequent observation shows that the reversal of serologic reactions is permanent, nonspecific measures are not warranted. It should be borne in mind, however, that the patient with the least parenchymatous degeneration is the one in whom the most pronounced remissions will develop. It is my practice to treat intensively patients with

asymptomatic neurosyphilis with arsphenamin or tryparsamid or intraspinal methods and mercury or bismuth, for at least two full courses. If the serologic reactions do not show evidence of favorable progression the nonspecific measures are recommended, probably to be followed by the resumption of the accepted antisyphilitic medication.

Case 4.—A man aged thirty-four years had acquired syphilis seven years previous to coming to the clinic in August, 1923. At the time of admission the outstanding features were essentially as follows: In September, 1922 he had had two convulsions followed the next day by a spell of unconsciousness which lasted fifteen to twenty minutes. Since that time there had been periods of delirium followed by irrational periods. About two or three weeks following the onset of the first convulsion, he became violent, and was agitated and out of his mind so that it was necessary to place him in an institution, at which time the diagnosis of neurosyphilis was made and neoarsphenamin and mercury intramuscularly were given. The Wassermann reaction on the spinal fluid was strongly positive; the Nonne reaction was positive. There were 29 small lymphocytes, 19 large lymphocytes, 9 polymorphonuclear leukocytes, and the colloidal benzoin reaction was 112 200 333 321 200. A diagnosis of early paresis was made and a course of alternate intravenous and intraspinal treatment was started. The patient received a total of twenty-seven injections of tryparsamid in a period of about one year. At the end of this time he was still demented and was inoculated with *Plasmodium vivax* July 20, 1924. Six months later his home physician gave him nine intraspinal treatments and a corresponding amount of mercury, and a year after the treatment by malaria he had again started to work. His memory was still poor but he was able to earn enough to be self-supporting. The Wassermann reactions on the blood and spinal fluid had become completely negative but he was by no means in a complete remission. He required more or less supervision because of the marked irritability. Two or three months after the course of malaria, although the reaction on the spinal fluid had been negative for a period of six months, a series of typical paretic convulsions developed during which he died.

Reversal of serologic reactions following treatment by malaria is not necessarily an index of clinical improvement in parenchymatous neurosyphilis. I have observed cases in which the reversal was complete shortly after the course of malaria but in which unfavorable clinical progress was manifest. I much prefer to note clinical improvement developing irrespective of the serologic reactions, because in 82 per cent of the cases in which complete remission developed, negative reactions eventually developed in the spinal fluid and blood. Treatment by malaria

has not as yet been established as a means of curing patients with general paresis, but the accumulated experience affords indisputable evidence that it produces a higher percentage of economic remissions in patients with general paresis than other methods available at this time. So in interpreting these remissions, the clinical status of the patient and not the serologic data is the paramount factor.

Case 5.—The patient was a railroad engineer who, when admitted to The Mayo Clinic in March, 1925, was found to have general paresis. He gave a definite history of having acquired syphilis fifteen years previously and had received a desultory amount of treatment at the time of acquiring the infection. At the time of admission to the clinic he complained of extreme weakness and mental changes. His family had noted increased forgetfulness, marked emotional instability with spells of depression and crying, difficulty in walking, apparently not a true tabetic ataxia but more a clumsiness which resulted in frequent falling, a marked decrease in strength with associated intention tremor and twitchings about the mouth, with some slurring speech. The Wassermann reactions on the blood and spinal fluid were strongly positive. The Nonne reaction was positive, there were 25 lymphocytes, and the colloidal benzoin reaction was 113 333 333 333 100. The neurologist made a diagnosis of general paresis. The patient was inoculated with *Plasmodium vivax* in March, 1925 and had a series of fourteen severe paroxysms without complications. Six months later he was given a course of intraspinal treatment in conjunction with mercury arsphenamin and sodium iodid intravenously and intramuscularly. He received three similar courses of combined intravenous and intraspinal treatment at intervals of four months, in addition to mercury inunctions in the interim at home. The last examination of spinal fluid, in January, 1928, was completely negative. The patient, however, is unable to retain a position. He is forgetful, confuses the date of Armistice Day with that of the Fourth of July, is unable to multiply even the simplest figures, and mental deterioration has been progressing slowly and steadily. He is not troublesome. His wife supports him and he has about enough mentality to wash the dishes and do the chores about the home.

This case is an example of the slow mental deterioration, occasionally seen after treatment by malaria, although the serologic reactions have been reversed to negative. There was a decided change in the patient's personality; the irritability and agitation had disappeared and in their place a rather quiet unassuming type developed. He could not assume any responsibility but had some insight, although dependent on relatives to make practically all of his decisions for him. This patient

might justly be classified as improved because for more than three years it has not been necessary to place him in an institution. Neither has he been a charge on the community, and although he is not an asset to his family, he is probably less of a burden than an untreated patient with a similar degree of degeneration. It is obvious that treatment by malaria was given to this patient too late as at the time of inoculation considerable irreparable degeneration had already developed. I would not dispute the fact that this treatment in such a case would not have been warranted if it were not that I have observed patients in whom the definite signs of paresis had been well marked for several years and sufficient remission followed the treatment to enable the patient to maintain a menial position and help to support his family. In other words I believe patients with indisputable signs of general paresis are also entitled to a course of treatment by malaria because it is not yet possible to forecast which patients will derive benefit and which patients will not. In the markedly advanced cases in which the patient has been leading a vegetative existence in an asylum for several years he is invariably made worse by this form of treatment.

COMMENT

These five cases are presented to demonstrate the favorable and unfavorable clinical result of treatment by malaria and to direct attention to the significance of the serologic changes in both the blood and the spinal fluid. Attention is called to the ideal type of case for such treatment, namely, that of so-called asymptomatic paresis in which the intensive use of antisyphilitic remedies has failed to maintain negative serologic reactions or to reverse them to negative. My experience warrants the use of the treatment in this type of case before obvious clinical signs of parenchymatous neurosyphilis develop.

THE PAIN OF TABES DORSALIS

HARRY L. PARKER

IN listening daily to the complaints of the sick one is ever reminded of the words of Saint Paul: "There are it may be so many kinds of voices in the world and none of them is without significance. Therefore, if I know not the meaning of the voice I shall be unto him that speaketh a barbarian and he that speaketh shall be a barbarian unto me." Those unfortunates who seek relief from pain can only in their own tongue describe their sufferings; it is the duty of the physician to comprehend their mode of expression, to appreciate the source from which their complaint arises and above all to estimate its relative intensity. Too often an error is made in misinterpreting the complaint in terms of the examiner's own preconceived ideas, or in suggesting to the patient a story grossly inexact both in form and substance. Truly are we often barbarians in the Paulian sense of the word and it is this inability to descend or rise to the patient's intellectual level that makes us so.

In such a disease as tabes dorsalis the patient may complain of many subjective symptoms. Frequently they are bizarre, unusual and tinged by the patient's own ideas on the subject and yet many are characteristic and almost pathognomonic of the disease and may lead to a rapid and efficient understanding of the underlying pathologic process. Such understanding may save the examiner infinite trouble and lead him into advising an efficient treatment early and thus avoid the patient's being sidetracked into some line of investigation or treatment leading nowhere. It is, therefore, worth while to review a group of cases each one demonstrating a more or less characteristic feature of the disease, especially from the standpoint of the patient's history.

"LIGHTNING" OR "SPOT" PAINS OFTEN THE EARLIEST AND THE PRESENTING SYMPTOM

Case 1.—A man aged forty-five years came to The Mayo Clinic September 25, 1928 complaining of severe pain in the lower extremities. Seventeen years before examination he had contracted chancre of the penis. Immediately afterward three injections of salvarsan were given intravenously and from that time further treatment had not been given. He had considered himself cured up to six months before his visit to the clinic, when for the first time he experienced severe, sharp, sudden pain in the lower extremities, wrists, and forearms. The pain seldom lasted longer than the time that it would take to count three. It was severe enough to make him wince and if he experienced pain while walking it would almost "strike the legs from under" him. The pain was usually confined to a small area about 3 cm. in diameter and it might appear anywhere in all four extremities, more frequently, however, in the lower extremities. The attacks lasted from five or six hours to two days. Usually at such times one area was picked out, for example, the heel or great toe, front of the thigh or ulnar border of hand, and in that area and for that period the pain recurred every few minutes. During the attacks the particular area involved was extremely sensitive to light touch but was not affected by deep pressure. Rarely, for the particular attack, the pain might change its site and continue also in other areas. Following an attack there might be a period of remission with complete freedom from pain three weeks to a month. The patient described the pain as being like the "thrust of a knife" or another time as being like "the touch of a red-hot electric wire." Certain factors tended to bring on an attack, such as changes in weather, and he was particularly likely to suffer just before a storm. Frequently the attacks came at night interfering with sleep.

The patient was thin and undernourished. The blood Wassermann reaction was strongly positive; the spinal fluid also reacted positively and contained 95 small lymphocytes, 17 large lymphocytes, and 3 polymorphonuclear leukocytes for each cubic millimeter of spinal fluid. Vision and eye-grounds were normal; typical Argyll-Robertson pupils were present. There was slight sensory change to pin pricks over the lower extremities with delayed sensibility.

This case is a fairly good illustration of the pain that appears early in the course of tabes dorsalis. Frequently such pain may be present for many years before other symptoms develop and be wrongly diagnosed "neuritis," "rheumatism" or some such name, while its true significance is overlooked. The attacks of pain usually last from twelve hours to a few days and then spontaneous remission occurs, leaving the patient free from pain for weeks or months. For this reason patients are likely to bear the attacks philosophically and not seek reputable advice until they have suffered for months or years. Also questioning

a patient during a free interval may not produce a history of attacks for he may have either forgotten them or but vaguely remember them. The sharp localization of the pain to small areas has led to its being called "spot" pain perhaps a name preferable to the time-honored one of "lightning" pain. The small area of attack, the sudden onset of pain and the duration of not more than a few seconds is characteristic. Patients find it hard to describe the quality of the sensation, however much they are impressed by its intensity. It is often described as "shooting," "darting," or "jabbing." Seldom is the word lightning used; that is more the description of the examiner who has never felt the pain. Such similes are used as being "stuck by a knife," "struck by a hammer," "shocked by a hot electric wire" or "a red hot spike thrust into the flesh and held for a second and then removed." Usually the pain is severe enough to make the patient flinch, to draw his breath in sharply or to cry out or swear and while walking on the street should a pain strike him he may stop involuntarily for a few seconds. The hyperesthesia described in this case is not constant, but frequently the patient complains of the area struck as becoming "sore" after a series of attacks of pain. Movement does not influence the pain; it comes whether the patient is walking, sitting or standing, or it even awakens him from sleep. An attack of pain frequently accompanies a storm or damp cloudy weather and being often relieved by aspirin makes the patient doubly sure that his pains are rheumatic in character. A spinal puncture, a few injections of salvarsan or even the more modern treatment by malaria or typhoid fever vaccine may induce a severe attack. Finally, in describing his symptoms, the patient generally goes through a series of motions that are characteristic in themselves. He may place one foot on the other knee and, with his index and middle fingers, make a pointing or jabbing motion to a small area such as the great toe, the heel or a spot on the calf or thigh. He may also bend over and make a motion with his index finger as if skewering the muscles of his leg with it or he may pinch the ulnar border of his hand with the thumb and forefinger. He may grasp his thigh muscle vigorously and

confidently to show there is no pain on deep pressure but he dares only to stroke the skin gently, and with an expression of anguish he demonstrates the hyperesthesia or he may tenderly pull the cloth of his trousers away from the sensitive spot to relieve the skin from such contact. The pain is characteristic and quite constant for tabes dorsalis. The only other disease in which there occurs even the most superficial resemblance to such pain is diabetic neuritis in which, at times, the resemblance may be very close. Occasionally it may be impossible to distinguish between tabes dorsalis and diabetic neuritis; tabes dorsalis and diabetic neuritis sometimes occur simultaneously. In any event, excluding diabetic neuritis, the pains are almost pathognomonic for tabes dorsalis and hearing of their occurrence should be sufficient to initiate an investigation in that direction.

Although the spot pain is the more common feature in tabes dorsalis occasionally the pain takes on a linear character in radiation, especially along the posterior aspect of the thighs, and the patient indicates its extent by drawing his forefinger along a line several centimeters long. Occasionally it may radiate the whole extremity. The association of the attacks of pain with various skin lesions, such as herpes, or purpuric spots, is not uncommon.

PAIN ALONG THE COURSE OF SCIATIC NERVE AND IN THE PERINEUM ASSOCIATED WITH HERPES GENITALIS

Case 2.—A man aged thirty-eight years came to The Mayo Clinic August 23, 1927, complaining of severe pain in the posterior part of both lower extremities and the hips. He admitted having had a primary syphilitic lesion twenty years before and had had more or less desultory treatment since. Two years before admission, about every month for seven to ten days he suffered from severe jabbing, sharp pains down the posterior part of the thigh. These pains would radiate along the line following the course of the sciatic nerve; sometimes the track of the pain would be only a few centimeters long. More recently the pains had been shooting the whole length of the extremity and down to the heel. A year before, the same darting, stabbing pains began to appear in the perineum and genitalia, and following the attacks a herpetic eruption would appear on the penis. During an attack light touch to the area involved was intolerable while deep pressure did not seem to have any effect. Between the attacks symptoms were absent.

Argyll-Robertson pupils and diminution of the left Achilles reflex were noted. The Wassermann reaction on the blood was strongly positive. The

reaction of the spinal fluid, however, was negative, but there were 3 small lymphocytes and 7 large lymphocytes for each cubic millimeter of spinal fluid.

Not only does the spot pain of tabes dorsalis frequently antedate all other symptoms of the disease by months or years, but it tends to continue throughout the course of the malady. More than that, it may remain a prominent and distressingly persistent symptom even when all signs of progress have ceased and even when the patient's blood and spinal fluid do not show signs of syphilis.

SEVERE TABETIC SPOT PAIN AFTER CESSATION OF PROGRESS OF THE DISEASE AND NEGATIVE SEROLOGIC TESTS

Case 3.—A man aged sixty-two years has been seen many times at The Mayo Clinic. His first visit was November 8, 1913. He had had a primary syphilitic infection in 1892. Sharp, shooting, spot pain had been present for twenty years, and had persisted without change in severity or frequency. He had been ataxic for seventeen years and had had Charcot's disease of the left ankle and knee joint for fourteen years. Incontinence of urine had been present also many years. The Wassermann tests on the blood and spinal fluid had been positive fifteen years before but on repeated tests since then they had remained negative.

Fairly advanced tabes dorsalis, Argyll-Robertson pupils, absence of tendon reflexes, Charcot's disease of the left ankle and joints, diffuse sensory changes and moderate ataxia were noted. A Le Riche operation (stripping the periarterial plexuses from the left femoral nerve) performed six years previously, had had no influence whatsoever. The severe pain occurred every few weeks in the arms and legs, an attack lasting three or four days.

Usually the appropriate treatment for central nervous system syphilis checks the attacks or ameliorates their severity. Occasionally, however, and particularly in long standing cases in which serologic tests are negative, as in Case 2, the disease is not influenced by ordinary forms of treatment. It is to be hoped, however, that the more modern forms of fever treatment may have some influence on this distressing symptom.

Although spot pain occurs much more frequently on the extremities, occasionally it occurs in a typical fashion on the trunk and even on the face but usually the trunk pain of tabes dorsalis is of a more complicated nature, is less constant in character and consequently is likely to be a very puzzling diagnostic problem.

TRUNK PAINS AND MARKED SENSITIVITY OF THE SKIN OF THE THORAX AND ABDOMEN

Case 4.—A physician aged forty-eight years came to The Mayo Clinic April 3, 1922, because of severe pains surrounding the lower part of the chest and upper part of the abdomen. He denied ever having had primary syphilitic infection but admitted multiple exposures and two gonorrheal infections. The trouble of which he complained had appeared about twenty months before his visit to the clinic and in its earliest stages was a dull ache over the ensiform cartilage. This gradually became more severe and spread to involve the lower part of the thoracic wall and upper part of the abdomen equally on both sides between about the sixth and ninth dorsal segments. This pain was a constant, dull, squeezing type of sensation with, however, violent exacerbations of sharp, lancinating pains radiating in the lateral chest wall medially to the median line. Three months after the onset of these pains he suffered, during exacerbations, spasmodic contractions of the abdominal muscles tending to double him up. The contractions, however, lasted only three months, but the sharp, lancinating pains persisted and increased in severity. These had been severe up to a few months before his visit to the clinic but had lessened somewhat at the time he was being examined. Associated with the pain was intense hypersensitivity of the skin over the chest and abdomen, and a light stroke or touch in that area was intolerable to him. The friend who slapped him on the back was likely to be regarded as his bitterest enemy and treated accordingly. About eight months before the patient's visit to the clinic a spinal puncture had shown a positive Wassermann reaction, with 27 cells in each cubic millimeter of spinal fluid. The blood Wassermann reaction at the same time was also strongly positive. He had been put under energetic antisyphilitic treatment previous to his visit which in part may have been responsible for some of the amelioration of symptoms.

On examination a zone of anesthesia to pain, tactile and thermal, over the chest and back from the third to the sixth dorsal segments was noted. Above and below this area there was intense hyperesthesia to cold or hot stimuli and to stroking with a sharp object, such as a pencil or a finger nail. In the lower extremities there was diminution to pain and thermal sensibility. There was also a distinct delay in appreciation of stimuli in that area. A pin prick over the leg, for example, might not be appreciated the moment it was administered, but the sensation might a few seconds later be felt fairly distinctly. The left patellar reflex was definitely diminished, although present, and both Achilles' reflexes were hard to obtain. Vibration sensibility was markedly reduced over both lower extremities and the iliac crests. The blood Wassermann reaction was negative and the spinal fluid reaction was also negative with 4 small lymphocytes for each cubic millimeter.

UNILATERAL TRUNK PAIN ASSOCIATED WITH MORPHINISM; HYPERESTHESIA OF SKIN, ABDOMEN, AND NECK

Case 5.—A woman aged forty-one years came to The Mayo Clinic July 21, 1925, because of pain in the back. At the age of sixteen years she had been married to a dissolute man and after two years she became separated from him

because of nonsupport. Fourteen years before examination she began to complain of pain in the middorsal region posteriorly just below the angle of the left scapula, that is, between the eighth dorsal and first lumbar vertebral spines on the left. This she described as constant soreness with exacerbations of flashing, hot lightning-like waves of pain lasting about a minute. Attacks came at intervals of about a year at first but gradually became more frequent and severe. She had been given morphin for relief, but whereas $\frac{1}{4}$ grain would relieve pain at first, later she became habituated to it and demanded larger and more frequent doses. She also complained of extreme sensitivity of the abdomen and back to touch and to thermal stimuli, and of sharp, shooting pain in the lower extremities coming at rare intervals and confined to small areas. When the pain in the back became very severe and was not checked by morphin, she became nauseated and vomited.

The patient was small and undernourished. Argyll-Robertson pupils, marked hyperesthesia to cold over the abdomen and chest and slight diminution of pain sensitivity over the area of the nipples were noted. Vibration sensibility was moderately diminished over the lower extremities. The Wassermann reactions on both blood and spinal fluid were negative and the cell count in the spinal fluid was normal.

Cases 4 and 5 had a great deal in common and they represent good examples of the type of pain under consideration. The only difference between them was that the patient in Case 5 had had pain for more than fourteen years and had become a morphin addict.

Pain on the trunk is often of segmental distribution and is especially common in part or all of the regions supplied by the third to the ninth dorsal segments. The pain may be bilateral as in Case 4 or unilateral as in Case 5. Because of the tendency of the pain to surround the thorax and upper part of the abdomen in the form of a band, the term "girdle pain" has been used. The pain may, however, be confined anywhere in a circumscribed area and it may even be in the median line. The character of pain is usually poorly described and often misleads the unwary into assuming that some local visceral organ is at fault. Commonly a constant "dull," "aching," "squeezing," "tight," or "drawing" sensation is complained of with exacerbations of flashing, darting, agonizing pain. The most common and most highly diagnostic feature is the associated, often intense, hyperesthesia of the skin of the abdomen and thorax. This, however, is common to all moderately advanced cases of tabes dorsalis.

The patients complain that their clothes irritate them; they cannot wear rough woolen garments over the chest or abdomen. Touching or stroking the skin is intolerable. They are particularly meticulous about the temperature of the bath water and do not tolerate marked ranges of temperature. It is a distinctive feature for a patient with tabes dorsalis to complain that in bathing in a lake or in the ocean that he can tolerate the cold water over his legs and thighs, but once it reaches the waist or chest it "cuts his breath off." Such a patient cannot bear to have the barber put hot towels on his face and when a spinal puncture is done the prick of the needle is better tolerated than the previous painting with alcohol. Normally the skin of the trunk is more sensitive than that of the extremities, neck, or face, but in tabes dorsalis this is exaggerated beyond all the bounds of normal. On examination, diagnostic proof that the condition has its seat in the nervous system, particularly in the posterior nerve roots, is well established by the association of zonal areas of anesthesia with areas above and below of intense hyperesthesia for the same stimuli. As in Cases 4 and 5 it is possible to find anesthesia to pain, thermal or tactile sensibility around the nipple zone unilaterally or bilaterally. Pain and thermal sensibility may be lost in one segment and tactile sensibility may be lost in a segment below it, but above and below these segments or alternating with them there is always a zone of intolerance to stimuli, particularly to heat and cold. There may be a zone of anesthesia dolorosa on one side in the region of the third, fourth, and fifth ribs; the patient may complain bitterly of pain and yet be anesthetic to all forms of stimuli. Light tactile sensibility may be lost but stroking with a match may be very disagreeable. Usually firm, even pressure is tolerated well; in other words, there is seldom any deep tenderness as in local disease such as myositis, cholecystitis, or gastric ulcer. Few and scattered clinical signs of syphilis of the central nervous system are commonly manifested in these cases which together with negative blood and spinal fluid Wassermann reactions, may make the diagnosis all the more difficult but for the characteristic alternating anesthesia and hyperesthesia described.

Although in Cases 4 and 5 there was little, if any, visceral disturbance associated with the pain, such disturbance, in the form of severe vomiting, may be a prominent feature as in the following case.

GASTRIC CRISES WITH ABDOMINAL PAIN

Case 6.—A woman aged forty-five years came to The Mayo Clinic October 31, 1928, complaining of pains in the back and abdomen and severe attacks of vomiting. Previous to her visit to the clinic she had had numerous abdominal operations without relief. The operations included appendectomy, cholecystostomy, cholecystectomy, and gastropexy. Five years before admission she began to suffer from pain in the middorsal region just below the scapula. This occupied an area in the median line about 6 cm. in diameter. The pain at first was intermittent, and two years previously it had become constant. She described it as "gripping" and "drawing." About the same time pain appeared in the back she also began to suffer from sudden, severe attacks of epigastric pain associated with incessant vomiting lasting as long as ten days. The vomiting was independent of food intake and between attacks digestive disturbances were absent. At the onset of the trouble she had double vision for six months and her eyes became crooked. She had lost weight, her usual weight being 140 pounds. At the time of examination she weighed 84 pounds.

The patient was weak and emaciated. The pupils did not react to light and very little to accommodation. There was partial paralysis of both external recti muscles and partial ptosis of both upper lids. Both patellar and Achilles' reflexes were abolished and there was marked hyperesthesia to thermal stimuli over the abdomen and back. Pressure pain was diminished in both lower extremities but there were no other sensory changes and she was not ataxic. The Wassermann reaction on both blood and spinal fluid was negative.

This unfortunate patient is an example of mistaken diagnosis and multiple unnecessary surgical operations. She had all the characteristic symptoms of the gastric crises of tabes dorsalis. Such an attack consists of sudden onset of prolonged, incessant vomiting with or without pain, and the attack ceases just as suddenly in twenty-four hours to ten days. The vomiting is independent of food intake and between attacks the patient does not have digestive disturbances and can eat all he pleases, usually regaining the weight lost during the attack provided the attacks do not come too often. Variations may occur but essentially the attacks are clear-cut crises without symptoms of visceral disease between attacks. Rarely, however, the tabetic

patient may have an associated gastric ulcer complicating the disease picture. Again, as in the presence of girdle pains, the hyperesthesia of the skin of the abdomen is very helpful in the making of a correct diagnosis. In cases of the gastric crises of tabes dorsalis, although there is no deep tenderness in the abdomen, hot or cold applications to the abdominal wall cannot be tolerated. A tabetic patient with gastric crises never seeks to alleviate his symptoms by using a hot water bottle or ice-bag. Heavy pressure, moreover, in the pit of the abdomen is not painful and actually the pain normally felt on the application of such pressure may be absent.

GASTRIC CRISES WITHOUT ACTUAL PAIN BUT WITH A PECULIAR SENSATION AROUND THE TRUNK DURING ATTACKS

Case 7.—A man aged fifty-one years first came to The Mayo Clinic September 7, 1922, because of repeated attacks of vomiting and pain in the lower extremities. At the age of twenty he had contracted a chancre and since then had had more or less continuous treatment. Twelve years before the first visit, and at intervals since, he experienced sharp, shooting pains, localized in very small areas in the lower extremities, particularly the heels, thighs, and knees. These had not been so severe during the previous one or two years. Eleven years before, he had had his first attack of severe vomiting, which came on suddenly in the middle of the night, and was believed to be due to ptomain poisoning. Since then, there had been repeated attacks, coming on an average of from two to three months, with three or four attacks in rapid succession over a period of a week or ten days. The onset of the attacks was associated with a feeling of intense squeezing or tightening over the upper part of the abdomen, as if the patient were held in a vise. This was not actual pain, but it was very disagreeable. There was also marked salivation, nausea, and vomiting; the attack came on more or less suddenly with incessant vomiting from six to twelve hours, and then gradually diminished. Between the attacks, gastro-intestinal symptoms were absent, appetite was not impaired, and although the patient iost weight during the attack he usually gained it back, for he ate ravenously of any kind of food during the free intervals. The pains in the lower extremities, and the attacks of vomiting were the only symptoms.

On examination the pupils were irregular; the right pupil was considerably larger than the left. They did not react to light, but reacted very well to accommodation The patellar and Achilles' tendon reflexes were abolished. There was a zone of anesthesia to tactile sensibility in the area of the right nipple and along the corresponding segment on the back over the shoulder blade. Around the same area, pain sensibility was also markedly diminished, as well as the power to appreciate temperature changes. Over the abdomen, however, was very intense intolerance to cold or hot stimuli. Over the

lower extremities, there was diminution to pain and thermal sensibility with preservation of tactile sensibility. Pain sensibility was distinctly delayed in its perception. There was also a moderate degree of diminution in pain sensibility over the forehead, nose, and cheeks. The Wassermann reaction on the blood was negative; that of the spinal fluid was at first positive, and it became negative on treatment; the last spinal fluid examination, three years later, gave negative results.

The patient has been seen from time to time during the last six years; the pain in the lower extremities has become much less severe, but the attacks of vomiting still appear at intervals of weeks or months as they have done in the last seventeen years. In spite of this, however, the patient has managed his affairs so that, by working during his well periods, he can earn a precarious livelihood.

GASTRIC CRISES OF TABES DORSALIS WITH PREMONITORY TINGLING OF THE EXTREMITIES AND "GIRDLE" SENSATION DURING ATTACK

Case 8.—A man aged forty-two years came to The Mayo Clinic November 9, 1920, complaining of attacks of vomiting. He admitted having had a primary syphilitic lesion sixteen years previous to admission. Two years before admission he had the first attack of vomiting. The intervals between attacks were frequently as short as two or three days and the attacks lasted from five to ten days. About fifteen minutes before an attack there was a premonitory sensation of tingling in the arms and legs, then suddenly violent nausea and vomiting. At the onset of an attack he also experienced an extremely disagreeable gripping tight sensation around the abdomen at the level of the epigastrium. He described his stomach as being "cramped tight." There was complete anorexia during an attack and he was unable to bear the smell of food. During an attack there was intense misery; he complained greatly of the tight squeezing sensation around the abdomen and feared impending death. The attack usually ceased as suddenly as it began; his appetite was immediately restored, and he ate ravenously. He had lost about 45 pounds in two years and had undergone appendectomy and gastroenterostomy without relief.

Examination showed Argyll-Robertson pupils, diminished Achilles' reflexes and a band of anesthesia to pin pricks across the thorax around the nipple zone. There was marked hyperesthesia to thermal sensibility across the abdomen and back. The Wassermann reaction on the blood was negative but that on the spinal fluid was strongly positive.

It is probable that most patients with tabetic gastric crises do not have pain in the real sense of the word. Careful questioning often reveals that associated with their attacks of vomiting instead of pain there is some bizarre sensation described variously as "a tight sensation across the abdomen," or "a feeling as if the chest and abdomen were being squeezed in a vise,"

"the stomach being cramped tight," or "a gripping feeling in the epigastrium." Cases 7 and 8 are, therefore, more typical of the gastric crises of tabes dorsalis than the preceding Case 6. Frequently, however, the patient in such crises does not experience local disagreeable or painful sensations, but complains simply of periodic crises of painless nausea and vomiting. Actually the nausea and vomiting is the outstanding feature of the gastric crises of tabes dorsalis.

There are no depths of the misery that are not plumbed by the tabetic patient. Essentially the disease is one replete with disagreeable subjective symptoms and there is also no limit to the intensity of suffering or the years during which it may continue. Furthermore, the number of different discomforts that any one patient can experience at one time are infinite. He may have all the sufferings described and yet still more to contend with.

LARYNGEAL AND RECTAL CRISES

Case 9.—A man aged forty years came to The Mayo Clinic August 4, 1922, because of spasmodic attacks of difficulty in breathing, pains in the limbs, difficulty in urination and unsteadiness in gait. He admitted having had a primary syphilitic infection ten years before admission, and two years before he had noticed difficulty in respiration on exertion and, on extreme muscular effort, a tendency toward loud inspiratory stridor. This had continued up to the time of examination and he was unable to take a deep breath on exertion. Later he found difficulty in expulsion of urine; it was hard to start the urinary stream and finally he had to sit down to urinate and press on the bladder with his hands. Twelve months previously he had experienced sudden, severe pains in the lower extremities, sharply localized in the area of attack. Four months previously he had had three attacks a week for six weeks when the larynx seemed to shut off suddenly and he inspired only with extreme difficulty. Some of these attacks came at night, waking him, and he would become cyanosed and walk the floor, hardly able to breathe. He became unconscious during one attack. During attacks of laryngeal spasm he made frequent movements like swallowing continuously. Suddenly these spasms would relax and air would enter with a loud stridor. The attack would end within five to ten minutes. While riding in an automobile or when working with his hands over his head he had frequent attacks of an intense desire to defecate and would attempt to do so with no result other than painful tenesmus and straining. Attacks of tenesmus came whether or not the bowels were empty.

Examination showed normal pupils, but both patellar and Achilles' reflexes were lost. The gait was slightly ataxic and there was diminution of

pain sensibility over both lower extremities with delayed sensation. The patient was markedly hyperesthetic to cold and to thermal stimuli over the abdomen. His voice was hoarse and laryngoscopic examination showed complete bilateral paralysis of both abductor muscles of the vocal cords. The Wassermann reaction on the blood was negative; that on the spinal fluid was strongly positive and there were 175 small lymphocytes for each cubic millimeter of spinal fluid.

COMMENT

A review of a series of cases such as the foregoing emphasizes the infinite variation in the symptoms and signs of tabes dorsalis. It is a clinical diagnostic term that has won acceptance by its convenience. As to how much or how little of symptoms and signs are covered by the term is a matter that cannot be stated definitely. No one symptom or sign is absolutely diagnostic and one patient may present a very different clinical picture from another and yet merit the term as applied to the disease. Furthermore, at one stage of neurosyphilis the patient may exhibit signs of tabes dorsalis and later exhibit signs necessitating the use of the term taboparesis or general paresis. Tabes dorsalis, however, is a convenient clinical term and may be used with reservations. There are a few outstanding complaints in the disease and diligently sought for they may be found. All that is needed is to lead the examiner on the right track of the underlying cause of the symptoms, namely, syphilis of the central nervous system. If such a conclusion can be reached early, definite headway is made in the appreciation, interpretation, and correct evaluation of the symptoms of disease of the central nervous system.

FURTHER STUDIES ON THE USE OF DIURETICS IN CARDIAC EDEMA

EDWIN G. BANNICK AND NORMAN M. KEITH

IN the last few years several valuable additions have been made to the list of diuretics used in the treatment of edema. Further practical knowledge as to their action has shown that their combined use is usually without toxicity and augments the single diuretic effect of each.

Three of the newer substances that in our experience have been efficacious in difficult cases of cardiac edema are the organic mercury compounds (merbaphen and salyrgan), euphyllin, and certain acid-producing salts, particularly ammonium nitrate. Saxl and Heilig, in 1920, introduced and successfully employed merbaphen in the treatment of cardiac dropsy and emphasized the fact that it was especially useful in such cases. Their observations have been confirmed repeatedly. At the present time a similar but less toxic compound (salyrgan) is more generally employed with even better diuretic effects. The xanthin diuretics have long been used in such cases, sometimes with marked benefit, and euphyllin is a valuable addition to this group, because it is, as a rule, well tolerated and is a potent drug.[3] Much has been written about certain acid-producing salts in various forms of edema and many have used them. In this brief report, we wish to emphasize again their value in edema due to cardiac disease. Of this group, we prefer ammonium nitrate.[1]

The following cases have been selected as typical examples of extensive edema due to cardiac disease and illustrate the useful part these diuretics can play in their treatment.

REPORT OF CASES

Case 1.—A man aged sixty-six years registered at the clinic November 14, 1928, complaining of shortness of breath, cough, and dropsy. Untoward symptoms had been first noted two years previously, at which time he con-

sulted a physician because of nervousness and shortness of breath; his blood pressure was high. A period of improvement followed which lasted until two and a half months before admission, when dyspnea became more pronounced and edema of the legs and ascites developed. The condition became progressively worse in spite of persistent attempts at treatment. For the last twenty-four hours he had been orthopneic and the cough had become much more distressing.

On examination slight ascites and general anasarca were noted. The area of cardiac dulness was greatly increased, due to hypertrophy and dilatation, and a roentgenogram of the chest showed a greatly enlarged heart. The heart tones were of poor quality and there was auricular fibrillation with systolic murmurs at the apex and base. There was marked congestion of the lungs, liver, and kidneys with fluid at the base of the right lung. The systolic blood pressure was 210 and the diastolic 140. Arteriosclerosis was demonstrable at the radial arteries and there was moderate sclerosis of the retinal arteries, with slight retinitis. The Wassermann reaction was negative. The urine contained a moderate amount of albumin. The phenolsulphonephthalein return was 30 per cent in two hours, the blood urea was 56 mg. and the creatinin 1.2 mg. for each 100 c.c. The electrocardiogram showed a rate of 100, auricular fibrillation, left ventricular preponderance, and diphasic T wave in leads I and II. The diagnosis was: Cardiac hypertrophy and dilatation with auricular fibrillation, profound decompensation, passive congestion of the lungs, liver, and kidneys, and generalized arteriosclerosis with early malignant hypertension.

The patient was given a diet of 2,000 calories and 40 gm. of protein, which was low in salt and water. He was given 6 gm. of ammonium nitrate daily, and on the second, third, and fourth days was given injections of small amounts of salyrgan, as indicated in Figure 250. Striking diuresis resulted. Following the first injection of 1 c.c. of salyrgan, the patient passed 6,700 c.c. of urine in less than twenty-four hours. The edema and ascites disappeared rapidly, so that at the end of seven days there was practically no edema; the weight had dropped from 186.5 to 160.5 pounds, and symptomatically he was much improved. The blood urea at this time was 31 mg. and the creatinin 1.5 mg. for each 100 c.c. The patient was much less dyspneic and was able to rest comfortably. A slight cough persisted and a few days later a mild cold developed. This caused him to cough considerably again and we thought it advisable to give him tonic doses of digitalis, allowing the medication by ammonium nitrate to continue as before. In a short time he was again feeling much better, and at the time of dismissal, twenty-six days after admission, he was markedly improved and was able to walk around the halls fairly comfortably. His weight at that time was 155 pounds; edema had not recurred.

Case 2.—A man aged forty-three years entered the clinic December 7, 1928, complaining of swelling of the legs and abdomen, extreme shortness of breath, and an irritating, troublesome cough. This patient had first been examined at the clinic in February, 1921, at which time auricular fibrillation and a slight increase in blood pressure were noted: 165 systolic and 100 dias-

tolic. The weight at that time was 250 pounds. The electrocardiogram showed a rate of 150, with auricular fibrillation and right ventricular preponderance. A roentgenogram showed enlargement of the heart. A diagnosis of myocardial disease and obesity was made. The patient had reduced his weight and restricted his activities considerably and apparently had been in good health since his first visit up until shortly before this admission. His blood pressure had not been taken since his examination at the clinic in 1921. Three weeks before this admission a cold developed following exposure, and then he noted, in succession, cough, dyspnea, cardiac palpitation, edema of the ankles, and finally edema extending up the legs and into the abdomen.

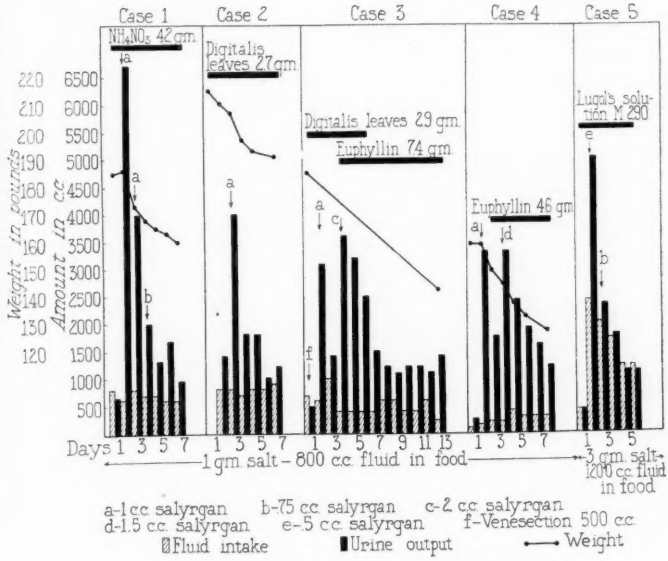
Case 1
Case 2
Case 3
Case 4
Case 5
NH4NO3 42 grm.
Digitalis leaves 27 grm.
Digitalis leaves 29 grm.
Euphyllin 74 grm.
Euphyllin 46 grm.
Lugol's solution M 290
Weight in pounds
Amount in c.c.
Days 1 3 5 7 1 3 5 7 1 3 5 7 9 11 13 1 3 5 7 1 3 5
1 grm. salt – 800 c.c. fluid in food
3 grm. salt – 1200 c.c. fluid in food
a-1 c.c. salyrgan b-.75 c.c. salyrgan c-2 c.c. salyrgan
d-1.5 c.c. salyrgan e-.5 c.c. salyrgan f-Venesection 500 c.c.
Fluid intake
Urine output
Weight

Fig. 250.—Diuresis in cases of cardiac edema.

On examination the patient was orthopneic, and was coughing up blood-tinged sputum. Moderate cyanosis and edema were present. The heart was markedly enlarged and showed auricular fibrillation. The pulse rate was 100 and there was an apical rate of 150. A loud, blowing apical systolic murmur was heard. The lungs were greatly congested, and the liver was enlarged and tender. The systolic blood pressure was 140 and the diastolic 115. Urinalysis was negative except for moderate albuminuria and a few hyaline and granular casts, and the phenolsulphonephthalein excretion was 50 per cent in two hours. The blood urea was 39 mg. and the creatinin 2 mg. for each 100 c.c. The Wassermann reaction was negative. An electrocardiogram showed a rate of 134, slight right ventricular preponderance and

auricular fibrillation. Examination of the fundi showed slight sclerosis of the retinal arteries of the hypertension type. The patient's weight was 215 pounds. The diagnosis was: Cardiac hypertrophy and dilatation with auricular fibrillation and profound decompensation, general arteriosclerosis with mild hypertension, marked passive congestion of the lungs, liver and kidneys, and obesity. It was decided that the cause was probably a combination of obesity, hypertension, and arteriosclerosis.

The patient was put in bed on a back-rest. Morphin and phenobarbital were given to promote rest, and a diet of 1,500 calories, which was low in salt and fluid, was ordered. Digitalis seemed to be definitely indicated because of the gross decompensation, the rapid fibrillation with pulse deficit, and the fact that the patient had never taken digitalis. Twelve grains of digitalis leaves were given daily at first. Because of the edema, it seemed that an additional diuretic such as salyrgan was indicated. On the second day, therefore, 1 c.c. of salyrgan was given intravenously, with immediate and satisfactory result (Fig. 250). Prolonged diuresis ensued, especially after the injection of salyrgan, and at the end of seven days the patient was free from edema. The weight had dropped from 215 to 191 pounds, and coincident with this there had been striking improvement in the patient's general condition. The pulse rate became slowed, although auricular fibrillation still persisted. The cough was diminished, dyspnea and cyanosis were controlled, and the patient felt greatly improved. The digitalis had been discontinued on the fifth day when a total of 42 grains of digitalis leaves (2.7 gm.) had been given. The patient was dismissed from the hospital on the fifteenth day.

Case 3.—A man aged sixty-eight years was admitted to the clinic July 23, 1928, complaining of shortness of breath, fatigue, general weakness, and marked dropsy. The trouble had apparently begun about two months before, when he had noted a general tired-out feeling with early fatiguability. About two weeks before admission he began to notice definite dyspnea, and at the same time the gradual appearance of the dropsy. A week before admission he had had some precordial pains, sharp and stabbing in character, radiating into the back. His condition had become progressively worse up to the time of admission.

The patient presented a picture of profound cardiac decompensation. He was orthopneic and cyanotic and was coughing blood-tinged, slightly frothy sputum. There was moderate edema of the abdominal wall with some ascites, marked edema of the legs and considerable edema of the scrotum and penis. There was moderate arteriosclerosis as estimated by palpation of the radial arteries. The heart was greatly enlarged, the left border being in the anterior axillary line. There was a loud apical systolic murmur, and slight cardiac irregularity due to premature ventricular contractions; the rate was 95. The heart-sounds were muffled and of poor quality. The lungs and liver were congested. The systolic blood pressure was 180 and the diastolic 110. The Wassermann reaction was negative; there was no anemia. Moderate albuminuria was present and the blood urea was 58 mg. and the creatinin 1.9 mg. for each 100 c.c. Examination of the fundi showed the

arteries to be of reduced caliber with senile fibrosis, but sclerosis was not marked. The diagnosis was: General arteriosclerosis and associated hypertension of the benign type with hypertensive cardiac disease and profound decompensation, and with chronic passive congestion of the lungs, liver, and kidneys.

The patient was placed in bed on a back-rest and given morphin and chloral hydrate as sedatives. The diet contained 1,500 calories and was low in salt and water. Because of the cyanosis, pulmonary congestion, and evident failure of the right side of the heart, venesection with removal of 500 c.c. of blood, was done immediately with great relief. Digitalis seemed indicated, especially in view of the fact that the patient had never had any digitalis, and he was given 9 grains of digitalis leaves daily. Because of the anasarca, further diuresis was desirable and two injections of salyrgan were given, with prompt diuretic response. This striking diuresis initiated by salyrgan was continued by the use of digitalis and euphyllin as indicated in Figure 250. At the end of two weeks the patient was entirely free from edema, his weight having dropped from 185 to 142 pounds, with a corresponding marked improvement in his condition. He was allowed to be up and about and was dismissed from the hospital on the thirty-first day, at which time he was able to take moderate exercise without appreciable dyspnea. With cardiac compensation restored, the blood pressure was approximately normal, ranging from 130 to 150 systolic and from 60 to 80 diastolic.

Case 4.—A man aged sixty-six years was admitted directly to the hospital September 3, 1928, complaining of marked shortness of breath and dropsy. He had had cardiac palpitation off and on for many years; the attacks had come on with or without exertion, but had not caused any disability until about six months before admission, when he noticed weakness. Shortly after this, following severe exertion, he became very dyspneic and had been somewhat short of breath ever since. Six weeks before admission he attempted to do some heavy farm work; marked dyspnea resulted, and two weeks later a severe attack of orthopnea occurred, lasting several days. Slight edema first appeared about the time when dyspnea was first noted, and this gradually increased. During the last month the legs had been markedly swollen and a week before admission abdominal paracentesis had been performed because of ascites which was again recurring rapidly. The patient had been taking digitalis for five months before admission, recently 15 drops of the tincture three times a day, and had been having a good deal of nausea and some vomiting.

On admission, the patient appeared extremely ill, a thin orthopneic old man with irregular respiration and slight cyanosis. The heart was enlarged with auricular fibrillation, and there was a slight pulse deficit. A loud, blowing apical systolic murmur was noted and some râles at the bases of the lungs, but there was little pulmonary congestion. The striking part of the picture was that of failure of the left side of the heart with marked anasarca and ascites. There was much arteriosclerosis as estimated by palpation of the radial arteries, and slight sclerosis of the retinal arteries. The systolic blood pressure was 170 and the diastolic 110. There was moderate albumin-

uria. Anemia was not present. Blood urea was 44 mg. for each 100 c.c. and the creatinin 1.6 mg. for each 100 c.c. Electrocardiogram showed auricular fibrillation with left ventricular preponderance and inverted T wave in leads I and II. The Wassermann reaction was negative. The diagnosis was: hypertensive and arteriosclerotic cardiac disease with auricular fibrillation, and marked failure of the ventricle with general anasarca and ascites.

The usual measures were employed to promote rest. The immediate problem in this case seemed to be the control of the edema. Inasmuch as the patient was nauseated and had been taking digitalis, it seemed that further administration of digitalis was not immediately important. The patient was given euphyllin in doses of 0.2 gm. four times daily, and injections of salyrgan intravenously were given as indicated in Figure 250. Profound and lasting diuresis resulted, so that in eight days the patient was free from edema, the weight having dropped from 159 to 127 pounds, with the general condition correspondingly markedly improved. A little later the patient was given tonic doses of digitalis and continued to be greatly benefited, although there was a slight accumulation of fluid which was again relieved by the injection of salyrgan. The patient was dismissed on the twentieth day free from edema and greatly improved.

Case 5.—A woman aged fifty-five years registered at the clinic September 12, 1928. The two outstanding symptoms that brought her to the clinic were dyspnea and dropsy. She had had similar trouble, seven years previously, for four weeks following a period of excessive work. She recovered from this fairly well, but always had some transitory swelling of the ankles, and slight dyspnea on exertion. Three years previously she consulted a physician because of vertigo, and he made a diagnosis of high blood pressure and kidney trouble. About two months before admission she had had right hemiplegia with difficulty in speech. She had been gradually recovering the use of her limbs, but since that time there had been more dyspnea and more dropsy. Recently she had been unable to lie down because of dyspnea and was scarcely able to walk for the same reason. She had noticed increased nervousness of late, with definite heat intolerance and weakness in the knees, and she had been losing weight in spite of a fairly good appetite and accumulation of edema. A troublesome cough had been a recent complication.

On admission, the first impression was that of profound cardiac decompensation. Orthopnea, slight cyanosis, and marked edema were present. On closer observation, however, there was clearly another factor present. The eyes were somewhat prominent, the palpebral fissures were somewhat wider than normal, there was slight stare, and the patient seemed unusually "jumpy" for the ordinary patient with cardiac decompensation. The thyroid gland was diffusely enlarged. A definite bruit was not heard over the gland but the examination was not satisfactory because of the dyspnea and rapidly fibrillating heart. The heart was markedly enlarged with rapid auricular fibrillation, pulse rate of 120 and apical rate of about 130 to 135. A loud, blowing systolic murmur was heard over the entire precordium, transmitted to the axilla and back. Diastolic murmurs were not heard. There was congestion at the bases of the lungs, and the liver was enlarged and tender. A

large umbilical hernia, slight ascites with marked edema of the legs and moderate edema of the lumbosacral region and abdominal wall were present. The hands and skin were moist and there was definite tremor of the fingers. Reflexes, as roughly elicited, were quite normal but there seemed to be slight residual weakness in the right arm. The systolic blood pressure was 190 and the diastolic 70; frequent examinations showed consistently a very large pulse pressure. Anemia was not present, urinalysis was negative, and the blood urea and creatinin were normal. A roentgenogram of the chest showed the greatly enlarged heart with definite passive congestion of both bases. The Wassermann reaction was negative. Electrocardiogram showed auricular fibrillation with ventricular premature contractions, right ventricular preponderance, diphasic T wave in lead II, and inverted T wave in lead III. Test of hepatic function with the bromsulphthalein dye showed dye retention, graded 3. The van den Bergh reaction was indirect and the serum bilirubin determination was normal. An unsatisfactory basal metabolic rate, early in the period of observation, was reported as +67, and a more satisfactory one six days later was +60. The diagnosis was: Obesity, exophthalmic goiter, benign hypertension, general arteriosclerosis, cardiac hypertrophy with chronic myocardial degeneration, auricular fibrillation, profound decompensation, and passive congestion of the lungs and liver.

The patient was given a diet of 1,800 calories and 50 gm. protein, which was low in salt and fluid, but it was difficult to keep the fluid intake as restricted as we wished because she did not coöperate well. She was given compound solution of iodin (Lugol's solution) in doses of 50 minims a day at first. Diuresis was desirable and we preferred not to use digitalis, so the patient was given small injections of salyrgan, as noted in Figure 250. Following the intramuscular injection of 0.5 c.c. of salyrgan the output of urine was 5,000 c.c. The diuresis was followed by prompt decrease in the edema; the diuretic, together with compound solution of iodin, was followed by marked improvement in the general condition, so that at the end of six days the patient was free from edema and markedly improved. Marked perspiration accounted for some of the water loss in this case. October 9 subtotal thyroidectomy was done; the pathologic report was hypertrophic parenchymatous thyroid gland. The patient had an uneventful convalescence and was dismissed from the clinic October 31.

COMMENT

The results of treatment in these cases illustrate certain facts worthy of further comment. In Case 5 a major operation was successfully performed within a comparatively short period after cardiac compensation was restored. All of the cases reported, and especially Case 5, show that striking and satisfactory diuresis can occur following relatively small doses of salyrgan. We believe that small doses given early and frequently repeated and combined with other diuretics cause more uniform and prolonged diuresis and are preferable in most cases

to large individual doses with a corresponding enormous periodic output of urine. This involves chiefly the important problem of adequate rest, which is a paramount factor in the successful care of the patient with cardiac disease. Urinary output of 10 liters in twenty-four hours indicates that the patient has not had sufficient rest. However, it should be kept in mind that in certain critical cases in which there is massive anasarca, immediate enormous urinary output may be the decisive factor in initiating the patient's recovery. The prompt benefit to the whole circulation in such cases is crucial.

Cases 2 and 3 confirm the well known fact that digitalis is a valuable drug in the treatment of cardiac decompensation, and may not be supplanted by any diuretics. But, on the other hand, the use of the latter may augment a digitalis effect and even produce a satisfactory result where digitalis had failed (Case 4). Such results would indicate that some of the beneficial effects of digitalis are due to a diuretic action as suggested by Withering in 1785. It is of interest that within the last few months we have observed a patient in the terminal stage of chronic cardiac decompensation, in whom periodic attacks of nocturnal dyspnea were not relieved by sedatives and digitalis, but were promptly controlled on several occasions following diuresis produced by injections of salyrgan.

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CARCINOMA OF THE SMALL BOWEL

J. ARNOLD BARGEN

Case 1.—A physician aged sixty-seven years was examined in the clinic October 5, 1927. About nine months prior to coming, he began to fatigue easily and appeared pale. Six months previously, however, the hemoglobin was 70 per cent (Tallqvist). About two weeks later it was found to be 45 per cent. The following day he fainted and passed tarry stools. Three months before admission *Endamœba histolytica* were found in the stools. Adequate emetin and arsenic treatments were without avail. Thorough roentgenologic study of the gastro-intestinal tract failed to disclose other cause of bleeding. Gastro-intestinal symptoms had not been present excepting slight distress from gas occasionally. Achlorhydria was noted. The tongue was sore and somewhat swollen at times; this was relieved by dilute hydrochloric acid. Frequent examination of the stools in the last six and a half months has always shown occult blood, and frequently tarry stools. Three transfusions in as many months, the last a week before admission, were followed by temporary improvement.

The patient appeared pale. His weight, usually about 155 pounds, was 153 pounds. The systolic blood pressure was 132 and the diastolic 70. The pulse was 88. Fever was not present. The hemoglobin by the Dare method was 36 per cent; the erythrocytes numbered 3,100,000 and the leukocytes 6,000. The differential count did not afford significant data. The total acid in the gastric content was 22, with absence of free acid, in an amount of 70 c.c. aspirated by test-meal. Neither parasites nor ova were found in the stools. The test for occult blood was strongly positive. The patient's blood belonged in Group 1. The Wassermann reaction on the blood was negative. Anemic optic disks were noted. Roentgenograms of the stomach, colon, and chest were negative. Proctoscopic examination did not reveal anything abnormal. A definite mass was felt in the left hypochondrium just above the umbilicus, October 8, and two days later, it could not be felt. The neurologist found slight evidence of pyramidal tract involvement, but in view of the absence of involvement of the posterior column and in view of the patient's age, evidence was lacking to permit the diagnosis of pernicious anemia. A diagnosis of an intra-abdominal lesion, probably of the small bowel, was made.

Exploration, October 17 (Judd), revealed annular adenocarcinoma of the jejunum which was resected and end-to-end anastomosis of the jejunum made. The postoperative course was uneventful.

Case 2.—A farmer aged thirty-eight years came to The Mayo Clinic September 16, 1928, complaining of attacks of diffuse abdominal pain, dis-

tention, vomiting, and anemia. He had been ailing somewhat for years and complained much of indigestion. Three years before admission he had had an attack of precordial pain, general ill feeling and dyspnea. His physician said he was anemic and that his ankles were somewhat swollen. He improved and was fairly well until February, 1928 when he noted swelling of the ankles and weakness. He had tired easily all winter. In May roentgenograms of the gastro-intestinal tract had been taken and his physician had remarked that there might be a tumor of the bowel. He was so anemic that pernicious anemia was suspected and he was fed much liver. Immediately after the roentgenograms had been made he had an attack of pain in the right side of the abdomen. In June he had a more severe attack accompanied by borborygmus, distention, and fecal vomiting. The bowels did not move for three days. Relief came after a hypodermic injection of morphin. Since then he had had many similar attacks and between the attacks the bowels were loose and watery. Several times there was questionable jaundice. With the attacks of pain, which usually localized about the umbilicus, there was usually profuse emesis although, fecal material was not vomited. He had had periods of severe epistaxis all his life.

The picture on admission was that of a pale, emaciated, dehydrated young man, suffering severely from abdominal pain and distention, and severe peristaltic cramps with loud peristaltic rumbling and visible peristaltic waves forming a marked pattern of intestinal obstruction. Tympanites appeared and disappeared. Edema was not grossly demonstrable. The spleen was not palpable. The tongue was not suggestive of pernicious anemia and a history of glossitis was not present. The patient's poor general condition made it seem advisable to postpone surgical procedures. Because of the apparent anemia and the possibility of two distinct pathologic conditions, careful study of the blood was undertaken.

The systolic blood pressure on admission was 84 and the diastolic 58; the pulse rate was 70 and the temperature 97.6° F. Repeated daily urinalysis did not show anything grossly abnormal. The Wassermann test of the blood was negative. The patient's blood was in Group 4. September 17, 1928, the hemoglobin by the Dare method was 44 per cent, with 2,400,000 erythrocytes and 2,900 leukocytes. September 19, the hemoglobin was 39 per cent, the erythrocytes numbered 2,460,000, and the leukocytes 2,200. September 26, the hemoglobin was 32 per cent, the erythrocytes numbered 2,300,000, and the leukocytes 1,600. On this day a transfusion of 500 c.c. of blood was given. September 28, the hemoglobin was 41 per cent, the erythrocytes numbered 2,540,000, and the leukocytes 1,300. Several differential counts showed 78 and 79 per cent polymorphonuclear leukocytes, 14 and 18 per cent lymphocytes, and a few transitional cells. October 2, the hemoglobin was 30 per cent, the erythrocytes numbered 1,940,000 and the leukocytes 1,100. Another transfusion of 500 c.c. was given. A daily blood count from October 2 to 4, inclusive, was similar to those recorded. The platelets ranged between 48,000 and 222,000 on various days. There was marked poikilocytosis and anisocytosis and polychromatophilia. The Lee coagulation time varied between seven minutes twenty seconds, and eight minutes thirty seconds. Bogg's coagulation time was four minutes. Calcium coagulation time was

eight minutes thirty seconds. The bleeding time, October 2, was five minutes and thirty-five seconds, and October 10 it was six minutes. The clot retraction time was two hours fifteen minutes. The volume index, September 20 and September 27, was 1.3 and 1.2, respectively. The prothrombin time was normal. The fragility test was within normal limits on two occasions. The reticulated cell count was 0.5 per cent at one time and 2.5 per cent a second time, and 1 per cent a third time. The blood urea, September 12, was 35 mg. for each 100 c.c.; October 8 it was 24 mg.; September 17, the carbon dioxide combining power was 56 volumes per cent, and the blood chlorides were 555 mg.

Roentgenograms of the chest and of the stomach and colon were negative. The fractional test-meal did not show free hydrochloric acid at the end of one hour and thirty minutes. The maximal total acidity was 14; there was no evidence of retention. Tests of hepatic function showed dye retention, graded 2; the van den Bergh reaction was indirect and the serum bilirubin was 0.8 mg. per cent.

A tentative diagnosis of an obstructive malignant lesion of the ileum or ileocecal region was made and exploration advised. At no time had the patient been in even a fair condition for surgical procedure.

In preparation for exploration intraperitoneal injection of a mixed vaccine of streptococcus and colon bacillus was made. Leukocytes did not increase. "Residue-free" foods were given and warm irrigations with sodium chlorid solution and, October 15, exploration (Rankin) revealed an annular obstructive carcinoma of the ileum. Resection and anastomosis of the bowel over a clamp was done. There was some free fluid in the peritoneal cavity. It was noted that the liver had a peculiar granular "feel," resembling that in cirrhosis. Metastasis was not noted.

The immediate postoperative course was uneventful. The entire abdominal wall showed extensive postoperative subcutaneous suggillations. Later ascites appeared. On the patient's dismissal from the hospital, November 17, his general condition had improved but the ascites persisted.

COMMENT

Intermittent attacks of intestinal obstruction with progressive anemia in the presence of negative roentgenograms of the stomach and colon should suggest primary malignant disease of the small bowel. Whether or not the barium meal would be helpful remains doubtful, because of the danger of obstruction, and the time of observations of the barium is difficult.

In both of these cases there were complicating factors. The achlorhydria was unexplained in both.

The blood picture in Case 2 was confusing. It is still a question whether blood dyscrasia was present, or whether the condition of the blood was a result of the long-standing anemia.

AMENORRHEA IN YOUNG WOMEN; HEMATOMETRA WITH UTERO-ABDOMINAL FISTULA

DELLA G. DRIPS

Usually cases of amenorrhea among young women may be classified in the group of so-called functional disturbances of the ovaries. Ovarian tumors, especially malignant neoplasms, may produce menorrhagia or metrorrhagia but occasionally cessation of the menses occurs, as in Case 1. Of course a careful pelvic examination reveals the probable cause of the amenorrhea if due to a tumor or to congenital anomaly. The most difficult differential diagnosis lies between functional ovarian disturbance and an early pituitary lesion. The young girl with a pituitary lesion may not have any complaint other than the amenorrhea and it may be two years or more before the headache and ocular symptoms which point to the lesion develop, as in Case 2. So in addition to a careful pelvic examination, it is well to subject such girls to an examination of the fundi and visual fields, to a basal metabolic test and roentgenogram of the sella turcica, with the hope of getting some clue as to the cause of the amenorrhea. The progress in each case should be followed. If these functional cases do not respond to the usual treatment the patients should be kept under observation and subjected to reëxamination from time to time.

Case 3 represents an unusual association of amenorrhea with uterine fibromyomas. The irregularity of menstruation apparently developed along with the tumors, since the patient's menses were regular and normal until three years before examination. The fact that the menses are again becoming scanty only a few months after the removal of the tumors indicates ovarian hypofunction as the cause. The normal function must have in some way been disturbed by the growth of the fibromyomas, probably through some change in the circulation.

REPORT OF CASES

Case 1.—The patient aged seventeen years registered at the clinic July 16, 1928. She complained only of amenorrhea which had been present for sixteen months. Menstrual periods had begun at the age of thirteen years and for several months occurred every twenty-eight days. The amount of flow was normal and the period lasted three or four days. Before the end of the first year, however, the periods began to come every two to three weeks, lasted only a day or two and were very scanty. Finally, sixteen months before admission, they stopped altogether. She did not have hot flashes. She had always been well except for influenza at the age of eight years, an occasional attack of tonsillitis, and headache at infrequent intervals. A younger sister had died at the age of eleven years following an operation for a large pelvic tumor which the father said had been diagnosed sarcoma of the ovary.

The general examination revealed the tonsils to be enlarged and infected. Pelvic examination revealed a hard, fixed, rounded tumor about 10 by 8 cm., in the posterior part of the pelvis. The cervix felt very soft and it was difficult to outline the body of the uterus or to separate it from the tumor. A diagnosis was made of a bicornute uterus with a tumor in one cornu or a solid tumor of the ovary.

At operation, a solid carcinoma of the left ovary was found. The tumor was not adherent and was easily removed. There was no evidence of metastasis. Only the left ovary and tube were removed. The pathologist reported solid adenocarcinoma, graded 4. Convalescence was uneventful.

Case 2.—The patient aged eighteen years registered at the clinic June 25, 1928. She complained of headache which had existed for two years, and amenorrhea which had existed for four years. She had had scarlet fever and influenza when a child. Menstrual periods had begun at the age of thirteen years. She had had a few normal periods and none for four years. Hot flashes had not occurred. Weight had gradually increased, especially in the last year. The headache had been present almost every day; it was usually present when she arose in the morning and many nights she had been unable to sleep because of it. It usually began across the bridge of the nose and spread over the head. The eyeballs ached but she had not noticed trouble in seeing. Vomiting had occurred with the headache only twice. The patient felt that she could think and remember as well as ever and neither she nor her family had noticed a change in her disposition.

The general examination revealed a well developed girl 5 feet, 7 inches tall and weighing 123 pounds. The breasts and external genitalia were well developed. There was no unusual distribution of fat over the body. Pelvic examination showed the uterus to be small and in a median position. The adnexal regions were normal. The systolic blood pressure was 110 and the diastolic 70. Pulse and temperature were normal. Examination of the eyegrounds revealed normal fundi; the fields showed a left temporal hemianopsia. The basal metabolic rate was −15. Roentgenogram of the sella showed enlargement of the sella, graded 3, with thinning of the clinoid process and calcified areas around the pineal body. The neurologic examination was objectively negative except for the left temporal hemianopsia.

A diagnosis was made of pituitary tumor and transfrontal exploration was advised. Intracapsular enucleation of the tumor was done. The pathologist reported adenocarcinoma, graded 1. The convalescence was essentially without incident.

Case 3.—A single woman aged thirty years registered at the clinic April 9, 1928. She had not menstruated for three months, and a lump in the right lower part of the abdomen had been noticed six months before. Menses had begun at the age of thirteen years. They were regular and normal until the last three years. About that time, they began to grow scanty and less frequent. Occasionally a period was skipped. The lump in the abdomen had seemed to increase in size with the menses and then to decrease to about the same size as when first noticed. For the last year, she had been having frequency of urination. She had been getting progressively more tired but thought this might be due to worry. She was contemplating marriage and was worried about not being able to have children.

On general examination several hard spherical masses could be made out in the lower abdomen and it was evident they had their origin in the pelvis. One mass extended about 5 cm. above the symphysis. Pelvic examination revealed the uterus to be enlarged and irregular. There was one nodular mass on the right that seemed attached to but separate from the body of the uterus.

A diagnosis was made of multiple subserous fibromyomas and one pedunculated fibromyoma, and exploration was advised with a view to doing a conservative operation if possible. At operation, the diagnosis was confirmed and multiple myomectomy was performed. The ovaries and tubes appeared normal. The convalescence was uneventful. November 27, the patient reported that since the operation her periods had been regular. The first two were fairly normal in duration and amount of flow, lasting four days with two days of free flowing. However, after that they had become more scanty, lasting three days with one day only of free flowing.

Case 4.—A woman aged thirty-two years registered at the clinic July 31, 1928. She complained of severe pain in the lower part of the back and through the lower part of the abdomen occurring at twenty-eight-day intervals and lasting three or four days. Four years before examination, she had been operated on because of "spotting" which had been occurring for three months between menstrual periods, especially after coitus. She wasn't sure about what had been done at the operation. She thought the cervix had been amputated and a portion of the body of the uterus removed. A median-line abdominal incision had been made. Following the operation, she did not menstruate but at regular twenty-eight-day intervals the severe pain, as noted, occurred. Because of this pain, a second operation was performed in March, 1928. At this time, an operation was done on the ovaries and tubes. The wound had been very slow in healing and had continued to drain through a small opening at the lower end of the incision until eighteen days previous to her coming to the clinic. The monthly pains had been much more severe since the second operation and some blood had come with the pus from the

small opening in the incision. She suffered from gas and bloating, frequency of urination, discomfort with bowel movements and bearing-down pain in the pelvis. She was very much upset nervously, crying much of the time. She said she had never been nervous prior to the first operation but since then had been very irritable and unable to control herself.

The general examination was essentially negative. At the lowest point of the abdominal incision there was evidence of the opening through which the pus and blood had come but it was apparently closed at this time. Pelvic examination showed that the cervix had been amputated. The uterus seemed to be of normal size. It was attached to the abdominal wall beneath the scar. In the posterior right side of the pelvis was a small, rounded mass which felt like a cystic ovary. A diagnosis was made of hematometra and utero-abdominal fistula. The patient was observed during a period of pain. At this time the uterus became fully twice as large and the abdominal fistula opened and discharged bloody fluid for several days. Pelvic exploration was advised.

November 7, 1928, subtotal abdominal hysterectomy was performed for intermittent hematometra and utero-abdominal fistula caused by the right tube being adherent in the wound. The left tube and ovary and part of the right tube had been removed previously. The right ovary was cystic and was resected, leaving tissue equal to about one-fourth of a normal ovary. The remaining portion of the right tube was also removed. The appendix had been removed. The convalescence was uneventful.

It is rather unusual for complete stenosis of the cervix to occur after amputation, as evidently happened in this case, since there was no menstrual discharge at any time following the first operation. Since there was no outlet for the menstrual discharge during the time between the first and second operations it must have accumulated either in the uterus or have been discharged through one or both tubes into the pelvic cavity.

THRUSH OF THE CERVIX UTERI; CERVIX UTERI AS A FOCUS OF INFECTION FOR CHOROIDITIS; FIBROMYOMA OF THE CERVIX UTERI; POSTOPERATIVE ADENOMYOMA OF THE ABDOMINAL WALL

L. Mary Moench

THRUSH OF THE CERVIX UTERI

A woman aged twenty-five years came to the clinic in August, 1928 because of diffuse and painful growths on the vulva and within the introitus. These lesions, of a papular nature, had appeared in July following a menstrual period and were associated with a painful eruption on the clitoris. The lesion at the clitoris disappeared but the condylomas increased in number and distribution and produced a distressing lancinating type of pain. The attending physician had considered the infection to be of a diphtheroid nature. She had taken douches of potassium permanganate twice daily without benefit.

Examination revealed scattered condylomas over the labia minora and forchette, ranging in length from 1 to 10 mm., and there were several small growths about the anus. Within the vagina these growths were confluent, involving the whole canal, the lateral aspects, in particular, in moist, papillomatous outgrowths bathed in tenacious mucus which clung like gossamer to the swab. On the anterior lip of the cervix appeared a gray membrane, 1 by 2 cm., of the same moist, glistening consistence, invading the cervical tissues, and which, when disturbed, produced oozing of blood from the underlying tissues. There was no enlargement of the inguinal lymph nodes. The temperature and the leukocyte count were normal and anemia was not present. There was no reason to suspect venereal infection in this case. The blood Wassermann reaction was negative. Smears from the lesion were negative for the gonococcus and for *Corynebacterium diphtheriæ*. A culture on Loeffler's blood serum yielded a profuse growth of yeast-like cells which on subculture in dextrose broth and Sabouraud's medium revealed pure culture of Monilia. The diagnosis of thrush therefore seemed the probable one on the clinical as well as the bacteriologic evidence. The condylomas, it would seem, developed in response to chronic irritation from the products of the disease process on the cervix.

The unusual site of this mycotic infection calls for an attempt at explanation. Yeast cells are occasionally encountered in cultures from the normal cervix, taken as a routine in the search for foci of infection. They are probably representatives

of the fecal flora or are air contaminants which have adapted themselves to cervical conditions. In these essentially normal cases they have seemed of little pathogenic significance. It is possible, however, that these organisms contain latent potentiality for virulence in direct relation to an assault on the body defenses, as is borne out by the fact that the majority of cases reported in the literature have occurred in association with pregnancy, anemia, or diabetes.

The patient in this case had been treated with roentgen rays in the clinic three months previous to the onset of this infection for a cervical adenopathy which was thought to be Hodgkin's disease. It is conceivable that the conditions underlying the pruritus of Hodgkin's disease may have rendered the mucous membrane less resistant to infection. The general defenses of the patient also had undoubtedly been reduced by a severe reaction to roentgen irradiation, and the resulting low threshold of immunity might readily yield conditions favorable for a change from saprophytic to parasitic growth. These organisms may therefore act as opportunists, as do certain of the streptococci, which under ordinary conditions flourish as harmless elements in the cervical flora.

References to cases of mycotic disease of the cervix and vagina are not abundant in medical literature. In 1909, Queyrat and Laroche reported a case similar to the one here described, which proved exceedingly resistant to treatment. A wide variety of antiseptics was employed without effect and only after a year creosote seemed finally to prove effective. As a result of cultural and animal studies these workers gave the name of *Parendomyces albus* to the organism isolated in their case. Yeast-like organisms found in association with genital lesions have also been described by Von Colpe, Gottschalk, Pollock, Van de Velde, and others. Castellani and Vuillemin have classified many of the Monilia associated with genital lesions.

As in the case described by Queyrat and Laroche, this case proved somewhat resistant to treatment. Formaldehyd in 2 per cent solution, which is specific in oral thrush, produced necrosis and extension of the process. The applications were

exceedingly painful and not tolerated by the patient. Mercurochrome and alkaline douches likewise were ineffective. In view of the gram-positive staining reaction of the Monilia and on the basis of Churchman's studies with bacteriostasis, a 1 : 1,000 solution of genitan violet was used, in topical application, and in douches. This treatment produced satisfactory clearing of the membrane within several weeks. The patient then discontinued treatment and returned to the clinic six weeks later, at which time the condylomas also had entirely disappeared and cultures from the cervix on the specific mediums were sterile.

CERVIX AS A FOCUS OF INFECTION FOR CHOROIDITIS

A single woman aged forty-one had been treated at the clinic in August, 1927 for exophthalmic goiter; thyroidectomy had been performed, following which her symptoms had subsided and her metabolic rate had dropped from +35 to −8 per cent. She returned to the clinic November 11, 1928. The complaint apparently was not related to the past condition. In May she had noticed an increase in the diplopia from which she had suffered for twelve years, and was conscious of a sense of stickiness in the eyes as if there were mucilage in them. In August her vision had begun to fail and she had consulted an oculist who examined her repeatedly and noted progressive failure of vision for which she stated that he did not assign a cause.

Examination revealed old central choroiditis of both eyes with evidence of activity in the macular region of the right. The oculist advised complete investigation for foci of infection. The tonsils had been removed in 1923; a bud of lymphoid tissue was found in one fossa which the laryngologist did not consider of focal significance. A roentgenogram of the teeth did not reveal evidence of periapical infection. The general examination and laboratory reports were negative except for the pelvis. There was nothing unusual in the pelvic history except a slight leukorrheal discharge to which the patient had not attached significance. The hymen was intact. The cervix contained a mucous plug with slightly excessive secretion which was cultured on three consecutive days. The fundus and adnexa were normal. Cultures from the cervical canal in dextrose-brain broth revealed staphylococci and streptococci from which a vaccine was made and, on the clinical and bacterial evidence, the patient was referred for coning out of the cervical mucosa. This was performed November 23 and December 3 the oculist reported subsidence of activity in the macular region and there was considerable subjective improvement. She was referred to her local oculist for the administration of vaccine and for observation.

This case is reported because of the satisfactory immediate result in response to eradication of a focus in the cervix in the

absence of other demonstrable foci. It is of course impossible to report this case as a definite cure without knowledge of the subsequent course. The case is one of a large series observed in the clinic since 1922, a group of which was reported in October, 1927 in which the cervix has been the only apparent focus in ocular inflammatory diseases and which have subsided following treatment similar to that outlined.

FIBROMA OF THE CERVIX UTERI

A woman aged forty-two years was referred to the clinic because of a large tumor of the cervix uteri. In March, 1927 subtotal abdominal hysterectomy had been performed elsewhere for multiple fibromyomas of the uterus. The convalescence had been uneventful but about six weeks after the operation a vaginal discharge of blood was noticed with increasing difficulty in micturition. Examination by her surgeon revealed the presence of a large vaginal tumor causing urethral pressure. He referred her for radium treatment following which the discharge ceased, but because of the size of the tumor and the obesity of the patient he hesita ed to carry out further surgical procedures.

Examination revealed a smooth, firm vaginal tumor about 10 cm. in diameter involving the entire cervix, the external os of which was represented as a crescent-shaped aperture impacted behind the pubic bone. It was incarcerated in the pelvic outlet causing partial obstruction to the rectum as well as to the urethra. Bimanual examination disclosed extension of the tumor into the right side of the pelvis. Because of the capacity of growth, sarcomatous degeneration of a cervical fibromyoma was considered. Biopsy, however, failed to confirm this conjecture. The size of the tumor was reduced by radium applied within the growth and roentgen irradiation over the abdomen and back, with relief of the obstructive symptoms. In two months abdominal exploration was performed and the tumor was removed by the abdominal route. It was found to be a cervical fibromyoma weighing 660 gm. The patient recovered uneventfully.

About 8 per cent of fibromyomas of the uterus occur in the cervix. This case is of further interest because of the rapidity of growth, and reduction in size following irradiation.

POSTOPERATIVE ADENOMYOMA OF THE ABDOMINAL WALL

A woman aged forty-one years came to the clinic because of lower abdominal pain of four years' duration. In June, 1923 perineal repair, and curettage and suspension of the uterus had been performed elsewhere. Eight months later, having previously been free from pain, she began to have severe pain in the lower part of the abdomen, in close association with the abdominal wall. It began with the onset of the menstrual flow, increasing in severity

as the flow progressed, and subsided gradually after its cessation until, for about a week before the onset of the next menstrual period, she was free of pain. The cyclic character of the pain and its situation in the region of the abdominal wall were interpreted as due to faulty uterine suspension. The uterus was resuspended, but the operation did not give relief.

Examination did not reveal an abnormal condition in the pelvis. On the abdominal wall, however, several deeply situated firm nodules could be outlined. The consistence of these masses and the cyclic character of the pain seemed to justify the diagnosis of adenomyoma of the abdominal wall.

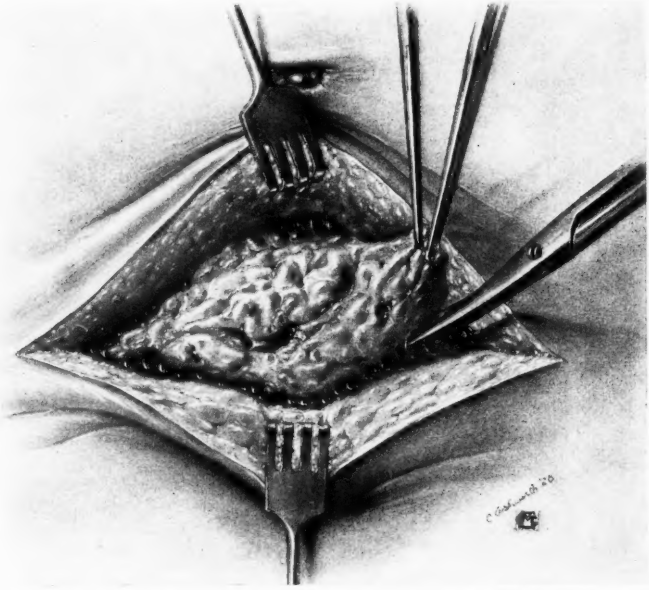

Fig. 251.—Adenomyoma lying beneath subcutaneous fat before removal.

At operation the masses were found to lie just below the sheath of the external recti muscles where it was assumed the round ligaments had formerly been attached, and measured 2 by 2 by 1 cm., the long diameter being parallel to the os pubis (Figs. 251, 252). A block of radium was applied over the operative site as a precaution against recurrence. Complete relief has resulted.

It was impossible to determine whether the origin of this ectopic adenomyomatous tissue was from the round ligament or from the peritoneum, or whether it served to illustrate Samp-

son's theory of "endometriosis." In 1925 Lemon and Mahle reported nine cases of adenomyoma of the abdominal wall from the records of The Mayo Clinic, in all of which a previous pelvic operation had been performed. Six of the operations had been of the nature of a uterine suspension. Of twenty-eight cases reviewed from the literature by Nicholson, fifteen had followed ventral suspension. Of the twenty-nine cases reported in 1925 from the literature by Heaney, fourteen followed ventral fixation. That these tumors could develop from an inclusion in the

Fig. 252.—Cross-section of adenomyoma situated beneath subcutaneous fat of the abdominal wall.

abdominal wall of a preëxisting adenomyoma of the round ligament or from the peritoneum is possible. Novak offered evidence that such tissue occurring in the umbilicus or abdominal wall may originate from the celomic epithelium of the urogenital folds. Origin from the normal endometrium of the uterus has been suggested and strongly supported by Sampson in numerous studies. He has shown that tubal epithelium may be transferred to a glass slide by brushing the fimbria of the fallopian

tubes over the surface of the slide, and that following curettage blood-containing bits of uterine mucosa escape at times from the uterine cavity through the lumen of the tubes. This "cellular spill" may be increased by operative manipulation of the uterus. He maintains that such tissue could readily find its way by direct implantation into the operative field and there develop into adenomyomatous tumors. The transplantation of endometrium by means of the surgeon's needle, as has been suggested, is possible, although Nicholson does not believe that it is probable that an ordinary needle could break off tissue and carry it for a considerable distance.

When such a tumor occurs it would seem best to follow surgical excision of the growth by a surface pack of radium. This serves as a precaution against recurrence as adenomatous tissue is itself radiosensitive and a shutting off of the capillary bed and the resulting sclerosis render the surgical field less favorable for a return of the growth.

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FOOD SENSITIVENESS AND CONDITIONS THAT MAY BE CONFUSED WITH IT

WALTER C. ALVAREZ

"Come W. Bowyer, and dined with us; but strange to see how he could not endure onyons in sauce to lamb, but was overcome with the sight of it, and so was forced to make his dinner of an egg or two."

"At table he did, they speaking about antipathys, say, that a rose touching his skin anywhere would make it rise and pimple; and, by and by the dessert coming, with roses upon it, the Duchess bid him try, and they did; but they rubbed and rubbed but nothing would do in the world, by which his lie was found."

"I bless God I never have been in so good . . . health . . . But I am at a great loss to know whether it be my hare's foote, or taking every morning of a pill of turpentine, or my having left off the wearing of a gowne."

Pepys' Diary, Sept. 5, 1664, July 12, 1666, and Dec. 31, 1664.

LET us picture a man who has been traveling, eating at restaurants, or dining out: suddenly he fills with gas, the abdomen becomes sensitive, perhaps there is colic, later diarrhea, and a crop of hives. His physician cheerfully concurs in the diagnosis already made, namely, that some article of diet has disagreed: but what was it? If during the preceding forty-eight hours berries or sea food were eaten they, of course, get the blame and everyone is satisfied; but what if no berries or oysters or crab were touched? What then?

Even the intelligent and careful observer who is subject to such attacks of intestinal irritation seldom becomes certain of what to avoid unless he is so highly sensitive to one or two foods that their ingestion, even in small amounts, always, and in a short time, produces distress. Usually he blames one food for

a while only to learn later that he can eat it with impunity. Perhaps he learns that fatigue and excitement play a large part in the upsets; that he can digest almost anything at home and nothing at a banquet where he is excited and fatigued by travel, by broken routine, and broken sleep. Under such circumstances food put into the stomach may remain almost untouched by the digestive juices, and several hours later it may be voided in loose, irritating movements.

A man who lunches quietly at home and rests afterward may digest with comfort foods which are eructed all afternoon when eaten in a restaurant, and particularly when eaten during the course of a business conference. Is this indigestion due to mental distraction and a lack of the priming psychic juice, or is it due to some difference in the way in which the foods are kept, prepared, or seasoned? Who knows?

But even the man who dines simply and quietly at home may, from time to time, experience digestive upsets, and may search in vain for a cause. He may for a day or two blame some article of food, only to learn, with the passage of hours that the flatulence, heart-burn, and regurgitation were prodromal symptoms of an approaching cold; or he may discover that the bowel which for days had appeared to be moving fairly satisfactorily, had really been filling with residues until, with the decomposition of this material, it became irritable enough to upset the functions of the tract above. With the passage of years, also, there may appear such symptoms as jaundice, severe colic, or hemorrhage, which will show that the attacks which were blamed first on one article of food and then on another were really flare-ups in the course of a long-standing organic disease.

For some time there have been good reasons for believing that intestinal upsets following the eating of spoiled food are much more likely to be due to infection with bacteria of the paratyphoid, paradysentery, or enteritidis groups than to poisoning with ill defined "ptomains." Most instructive is the case of an attorney from a small city in France who went to Paris to represent a client. While there he ate heartily of a meat pie sent him from home. Shortly thereafter he was seized with abdominal

cramps and other violent manifestations of food poisoning from which he soon died. The police investigated; a chemist thought he found traces of arsenic in the stomach, and although all the evidence indicated that the wife was a good woman, in love with her husband, she was condemned to the guillotine. All that saved her was the discovery by a bacteriologist that the pie was a rich culture of one of the dysentery producing organisms, and that she was a carrier. She had probably infected her husband's food on previous occasions, but never had there been such an opportunity for incubation between the time of cooking and the time of eating.

But often during the course of an attack of "ptomain poisoning" the most careful and expert bacteriologic study of liquid stools will fail to reveal any known pathogenic bacteria. What then? There are several possibilities. As K. F. Meyer reminds me, bacteria actively growing in the wall of the gut and producing disease there need not be present in the feces. Bargen can find a specific diplococcus in the lesions of most cases of ulcerative colitis but only occasionally can he find it in the stools.

Another explanation for some attacks of food poisoning may have been found recently by Branham, Robey and Day, and by Geiger and Meyer. In special mediums and under certain conditions some strains of paratyphoid bacilli produce thermostabile toxins which when given to mice in small doses by mouth, produce severe inflammation of the duodenum and small bowel and frequently diarrhea. The fact that this toxin is formed only under certain conditions of bacterial growth may explain the recent failure of Dack, Cary, and Harmon to produce indigestion in volunteers fed considerable amounts of boiled or filtered cultures of *Bacillus aërtrycke* and *Bacillus enteritidis*.

Another suggestion comes from d'Herelle who found that whenever, for a day or two, he had an intestinal upset with loose bowel movements, the lytic power of the bacteriophage normally found in the stools increased suddenly, and became specific for some one organism of the pathogenic intestinal group. As this is exactly what happens to the phage during a brief attack of

cholera or dysentery of known etiology it seems probable that the upsets that he experienced were due to infection with an organism which was destroyed by its phage before it could be cultured from the stools.

It is possible also that some types of irritable colon are associated with abnormalities in the excretory functions of this organ, and it is conceivable that flare-ups of mucous colitis are due to sudden increases in the quantity of some irritant that is constantly being gotten rid of by way of the large bowel. I have, at operation, examined the colon in a number of cases of long-lasting and severe mucous colitis and have been unable to see or feel any abnormality in it. In one such case in which a fine sensible young woman had spent much of her life on a couch with a hot-water bottle over the cecum, the right half of the colon was removed. The wall was somewhat thinned but so far as a good pathologist could see, the mucous membrane was normal. The patient is sure that she is better for the operation, and that the nervous symptoms are more bearable, but she is still on a couch with a hot-water bottle over the place where the cecum used to be. Evidently "mucous colitis" is not a true colitis but a "functional" disturbance somewhat resembling asthma.

It is customary today to say that such disturbances are due to imbalance in the sympathetic and parasympathetic nervous systems, but I have never been able to see that this makes us much wiser than we were before. We might with perhaps as much reason suspect that the discomfort is brought about by changes in the centers regulating defecation in the spinal cord or in the brain. I have been much interested in the discovery by Hatcher and Weiss that there is in the floor of the fourth ventricle near the vomiting center a remarkably sensitive area in which the application of such small amounts as 0.01 mg. of certain drugs will promptly produce diarrhea. One can easily imagine how in a nervous person an increase in the irritability of this center might bring the colon into the sphere of consciousness, and keep it there as a more or less constant source of annoyance and discomfort.

This center is probably developed in infancy during those months in which defecation comes under the restraining influence of the will, and it may well have something to do with the diarrhea of fright, nervousness, and perhaps hyperthyroidism. An over-irritability of this center may have been responsible also for the sad condition of a young woman who once consulted me on account of the tragic situation which threatened to keep her from ever finding a mate. Unfortunately for her, her nervous reactions to a little courtship always took the form of a call of Nature, so urgent that she was compelled to flee just at the time when it was most important to remain.

Other suggestions in regard to the mechanism of intestinal upsets have come through the work of Besredka who claims now to be able to immunize against typhoid fever, dysentery, and cholera by giving vaccine by mouth. He thinks the secret lies in giving at the same time bile which will increase the permeability of the intestinal mucosa. If he is right an increase in flow of bile might lead to an increase in the normal passage of bacteria into the lymphatics of the mesentery and perhaps an upset in intestinal function. Similarly K. F. Meyer (unpublished experiments) found that guinea pigs, normally immune to generalized infection with typhoid bacilli were susceptible when kept on a diet that led to the production of scurvy. Their susceptibility or immunity varied also with the acidity or alkalinity of their food. Similar observations have been made by Arnold (1928).

Some persons have told me that they could digest certain foods only if these foods were eaten alone. Thus an indigestible salad alone, gave no discomfort, but when eaten with a heavy meal of starches it apparently so interfered with the digestion of those starches that it caused flatulence and distress. Similarly the eating of much sugar with a starchy meal might, on account of the laws of mass action, make it difficult for the amylases to act, and the resultant distress might be wrongly attributed by the sufferer to the starches. Dietary faddists and quacks have written much about these incompatibilities of foods but I fear that little is really known about them.

Obviously, the way of the investigator in this field is going

to be hard. There is no question but that allergic indigestion is fairly common; one has only to look about one's circle of acquaintances to find several who become deathly ill or very uncomfortable after eating certain foods; the real question is: how many persons are there now passing through physicians' offices with mild manifestations of such poisoning, unrecognized and mislabeled? And if there are such, is there any way in which they can be recognized, and the offending food or foods identified? Enthusiasts about allergy claim many such cases as their own, but reading their reports makes me suspect that they are often dealing not with allergy alone but with combinations of food sensitiveness and various types of organic disease.

I regret that about all I can do at this time is to ask questions, but it may be helpful to present first, an interesting case in which I think allergy of intestinal origin was the principal source of trouble; second, a case of urticaria of unknown origin; third, a case of headache apparently due to the eating of cheese; and fourth, a few cases to illustrate the difficulties that beset the way of those who might be inclined to jump to conclusions.

A woman aged thirty-three, first seen in July, 1924, complained of severe headache, attacks of diarrhea, hay-fever, pains in the back and shoulders, urticaria, and frequency of urination. Both parents were frail. Her father suffered with loose bowels all his life and died with intestinal obstruction. The mother's immediate relatives were frail, and one of the mother's sisters probably had asthma.

All her life the patient's digestion was poor; she had had to choose her food with care; and from time to time, she had suffered with acute attacks of abdominal distress and mucous colitis. Until the age of twenty-four, she suffered with repeated attacks of pain throughout the abdomen, usually localizing in the region of the appendix. Appendectomy was performed, and a cystic right ovary was removed. The attacks of pain then disappeared, but she still had to be careful in eating.

Six or eight years before I saw her she began to have attacks of frequency of urination; the urine was examined repeatedly but nothing abnormal was found. "Bursting" headaches appeared at the age of twenty-six. Most of the pain was back of the eyes, but sometimes it was in the back of the head. The headaches came more and more frequently and were associated with dizziness and some nausea.

Three years before I saw her she began to have attacks of diarrhea, coming every three or four weeks. These attacks began and ended suddenly; the stools were generally watery, and they sometimes contained mucus and

blood. At the same time there often appeared crops of hives, sometimes hay-fever, and usually severe rheumatic pain in neck, shoulders, arms, and knees. Between attacks the bowel moved normally, but it felt sore and full of gas. Occasionally there was heart-burn, acid stomach, and belching; more rarely vomiting, and a gallbladder type of pain.

Both she and her physicians had long felt that the trouble was probably due to the ingestion of some food or foods, but although she is intelligent and had put much thought to the problem, she had failed to identify any particular offender. Her physicians had done the usual things: Appendix, tonsils, and teeth had been removed, but as sometimes happens, improvement had not resulted. Roentgenologic examination had shown stasis in the upper part of the small bowel.

Skin tests had been made by an earnest student of allergic problems, and pronounced reactions had been obtained with proteins from wheat, tomato, asparagus, and peas. These results would have been more satisfying if the patient had not reacted somewhat with almost every substance tested. She then avoided the foods that had given the strongest reactions, but, with the restriction of the diet, she became much worse: so ill, in fact, that for three years she was an invalid and much of the time bedridden.

General examination in 1924 showed a small under-nourished woman with tenderness of the neck muscles and the whole abdomen. Both kidneys were markedly floating. There was a small mass in the left broad ligament, probably tube or ovary. The blood pressure was normal. There was no dermatographia. Gastric acids were a little higher than normal. Parasites were not found in the stools. As she brought with her a portfolio full of films, laboratory reports, and opinions from able physicians, I did not examine her further.

As it seemed obvious that the woman was hypersensitive to foreign protein, and as treatment based on information secured from skin tests had failed to bring relief, I suggested that she start with a few foods and add to, or subtract from them according to the way in which she reacted. She began with beef, potato, milk, butter, sugar, and corn bread. On the fourth day there was a severe headache with rheumatic pain, irritable bladder, and irritable bowel. On the fifth and seventh days she broke out with crops of hives. For the next four days potato was eschewed but the symptoms continued unabated.

The eating of corn bread was then discontinued and for the first time in years there came a period of perfect health. Later, in order to make sure that we were on the right track, the patient ate corn bread and again suffered with the typical symptoms. Following that, she ate salad dressing made with corn oil and found this just as effective in producing the various types of distress. She then, for the first time, understood why so much of her trouble dated from the war. She was particularly fond of salad dressing and had always used an imported olive oil. When the supply from Italy was cut off, she began to use the newer types of salad oil made in America, and "the fun began."

Having once discovered some harmless foods it was fairly easy to experiment with others and to classify them as good or bad. The patient had, however, to keep a careful diary, because fatigue, colds, or excitement could still give rise to mucous colitis and sometimes rheumatic pain. Furthermore

small amounts of certain foods might be tolerated when larger amounts were not. For instance, an occasional egg was tolerated, but when eggs were eaten three times a day she soon experienced the old symptoms. Strange to say, strawberries gave her no trouble.

After a few months, the patient felt so well that she decided to go to Europe, and in order to avoid the inconvenience of having to go without bread while traveling, an attempt was made to desensitize her with injections of wheat-protein. This was fairly successful, but it was interesting to note that at one time, when an attempt was made to speed up the process of immunization, she experienced a severe attack with the old symptoms. During the following year she gained in weight from 100 to 135 pounds and experienced very few attacks of arthritis or colitis.

During 1927 her weight rose to 142 pounds and she was strong and perfectly well. There was no more colitis and only one attack of arthritis, following the taking of ginger ale. She then began again to experiment with foods and found that she could take with impunity small amounts of peas, tomatoes, and asparagus which previously she had been unable to touch. She was still unable to eat any corn, rice, raspberries, melons, almonds, or salmon. She still found it wise to avoid fatigue, worry, and strong emotion, and particularly wise to avoid eating when tired.

In January, 1928, there began a series of occurrences: the loss of a valued servant, the death of a friend, and an attack of influenza, all of which pulled her down and caused her to lose 20 pounds in weight. In April, arthritis appeared and in May an occasional attack of colitis. In June, with the appearance of hives, she stopped eating wheat and obtained relief not only from the urticaria but from much of the arthritis.

In July there came a return of the pain in the hypochondrium and there seemed little doubt about the presence of active cholecystitis. Unfortunately during the course of an examination by her physician she was given a large dose of magnesium sulphate which started up a "colitis" which kept her in bed most of the time for the next four months. This incident is a good example of the harm that we physicians commonly do as we put patients through routine examinations. I have seen so many disasters of this type following the purgation of such sensitive patients that I never order a cathartic until I have asked a few questions about the way in which the individual before me responds to such drugs. My caution may seem excessive but I know I can, by taking thought, spare many patients much discomfort; I know that I can thus avoid making enemies, and I know that I can avoid doing serious injury to those who have a tendency to colitis and diarrhea.

But to return to the patient: I heard recently that under a rest cure she is gradually picking up again, but the gallbladder is still tender and an operation may yet have to be resorted to. One wonders how much this cholecystitis has had to do with the symptoms during all these years.

It was a great pleasure in 1924 to see this almost bedridden invalid become a useful, happy member of the community, and naturally the experience made me wonder the more if I were not

missing other such cases, perhaps milder and less obviously allergic in origin. If there are such, surely I must be labeling them with such names as mucous colitis, fatigue neurosis, appendicitis, and cholecystitis.

During the next few years I watched carefully for suspicious cases, and everyone who came complaining of hypersensitiveness of the bowel, mucous colitis, or indigestion of vague nature, was tested with the various proteins. I soon found, however, as others have, that those tests are seldom helpful, and I was compelled to fall back more and more on home detective work and attempts to discover the source of irritation by a process of elimination.

In Rowe's experience the commonest food to give an allergic reaction is wheat, and after it follow in order eggs, milk, chocolate, tomato, cabbage, orange, potato, strawberries, walnuts, oats, and carrots. Obviously it is almost impossible for a patient to recognize sensitiveness to the first three foods because they are eaten with almost every meal. Another difficulty is that a man who has always eaten with impunity a food like crab will suddenly, for a time, become sensitive to it. One wonders what can have happened to make the difference. It is known now that small amounts of undigested food like egg-yolk are engulfed by cells in the intestinal mucosa and passed through the wall into the lacteals and on into the general circulation where their presence can easily be detected by immunologic methods. If this is going on all the time the normal man must in some way be protected from deleterious effects. Perhaps at times the body becomes too highly sensitized, or the dosage is too large owing to the opening up of wider paths through the intestinal wall, as by the presence of burrowing parasites or open ulcers. Interesting are the observations that show that skin sensitiveness to foods comes and goes.

Some of the difficulties met with in attempting to solve these puzzles are illustrated by the case of an engineer, aged forty-two, who while in the Orient, suddenly became covered with itching wheals which kept him in misery for more than a year. No sooner was one crop of lesions gone when a new one would appear. Shortly before the hives appeared he had had an

attack of amebic dysentery, promptly cured, and a short spell of dengue fever. He was so tormented by the urticaria that he returned to the United States for careful study.

He was a strong, healthy-looking man, who except for an occasional sick headache had no complaint to make about his digestion. Roentgenologic examination showed, as in the preceding case, some stagnation of the barium meal in the duodenum and upper jejunum. The stool was heavily infected with trichomonas, but amebæ or cysts were never found. The skin responded strongly to a number of foods, but exclusion of these from his diet had no effect. He then took matters into his own hands and lived first for two weeks on buttermilk alone, and later, for a week, on lamb chops and bread. As neither of these experiments brought relief, we both became discouraged and he departed for a vacation which seemed to help him more than did the dieting. When I saw him again a few years later he told me that the trouble had gradually left him before he could gain any clue as to the cause.

Another engineer, aged thirty-three years, complained of severe occipital headaches which had bothered him for years. With some of these headaches his eyes became yellow and he thought he was on the verge of jaundice. Attacks came about six times a year, and lasted two or three days. He had little indigestion, but there was some belching and flatulence with the headaches, and with the last one there was a little nausea. Shortly before coming to see me he had, for a week, experienced distress in the epigastrium. There was also some soreness in the left lower quadrant of the abdomen, coming in spells and lasting for a few days. As a boy one eye had turned out; he wore glasses, and sometimes eye strain seemed to bring on the headache. Appendectomy, some time before I saw him, had failed to give relief.

The man was powerfully built and well nourished. The blood pressure was normal. The neck muscles were tender. A careful examination showed little to explain the headaches except perhaps the still somewhat unbalanced eye muscles. Again, the progress of barium through the small bowel was found to be slower than normal.

The man then began his detective work and before the year was out he was able to report that the noxious agent was cheese. He was very fond of this food and occasionally would eat heartily of it. Self denial gave him complete relief. Several years later he wrote that he had to avoid hard cheeses but that he could eat with impunity soft cheeses.

Less convincing is the case of a rancher, aged forty years, who also complained of headaches which came about an hour after meals. These had been troublesome for the preceding four or five years. Shortly after they began, it was found that the sinuses were infected and many operations and irrigations were done. After two years this condition cleared up but the headaches persisted. The fitting of glasses then helped for a time. The headaches were originally in the top of the head but later they were mainly frontal. They were never associated with indigestion. Constipation was the rule with him, and sometimes when this trouble was at its worst he felt some pain and soreness in the appendix region. Before I saw him tonsils and all devitalized teeth had been removed, without improvement. A suggestion that the origin of his troubles might be in the bowel was obtained from the

fact that his mother suffered with asthma and indigestion, and that he appeared to react allergically to eggs, bread, onions, and cantaloupe.

I found a well developed and nourished man with a mild degree of generalized ichthyosis. The blood pressure was normal. Roentgen-ray examination showed a peculiar intermittent spasm of the cap, and a gallbladder that did not fill with dye taken by mouth. I did not dare to diagnose cholecystitis because I could not elicit any history of pain or indigestion. The skin reacted strongly to asparagus, cabbage, wheat-leucosin, wheat-proteose, grapefruit, lemon, cantaloupe, peanut, buckwheat, ovovitellin, ovomucoid, and faintly to beef and cocoa.

These tests encouraged him to diet more strictly, and for a time he was able in this way to keep free from headache. He soon tired of restrictions, however, and yielding to his home surgeon's desires, submitted to the removal of gallbladder and appendix. He was told that the gallbladder was buried in adhesions and diseased. A few months later when he wrote me that he was well and eating with impunity all the foods that had previously given trouble I did not know what to make of the problem and could only wait for time to throw more light. Now after three years he writes that his health is better than before the operation but he is still so sensitive to a number of foods that he has to leave them alone. Infection in his sinuses has flared up again and his eyes are giving trouble.

Like Pepys, I cannot be sure yet whether the improvement noted was due to the rabbit's foot, the pill, or the leaving off of the gown. This uncertainty is met with again in the following case in which the neurotic and hypersensitive constitution of the patient so complicated the picture of disease and the problems of diagnosis that I was never impressed with the results that appeared to be obtained by treatment.

A woman, aged thirty-five years, came complaining of severe mucous colitis which had begun at the age of sixteen. As a child she once was jaundiced and after that had several bilious spells. Seven years before I saw her she had been cured for a time by the removal of the appendix. Later, with the return of intestinal upsets, there came pain and soreness through the neck, spine, and left thigh. The stools were always soft but rarely diarrheic. When they were most nearly formed she was always at her best (a point emphasized in papers by F. L. Burnett). The colon was always sensitive, and pain along its course sometimes woke her at daylight.

Urticaria was present at times, but never the irritability of the bladder that is seen sometimes with it. So far as she knew there was no one with asthma in the family. She knew that she was sensitive to onions and oatmeal, and that the eating of walnuts would give rise to giant urticaria. Part of one tube was removed at the time of the appendectomy, menstruation was painful, and she failed to conceive in eight years of married life. She had

left her husband two years before I saw her and had suffered with insomnia and many worries.

General examination showed a well developed, nervous woman. Movements of the neck were painful. There was some dermatographia. Blood pressure was normal. The colon was tender. The stool contained trichomonas and an unusual number of Welch's bacillus. The skin reacted to orange, banana, asparagus, tomato, nuts, and slightly to wheat. On a smooth diet which contained none of the suspicious foods she was much better. Later, the taking of a purgative brought on an acute attack with mucus in the stools and pains throughout the body. After she had become comfortable again with the restricted diet, she ate oranges and the old troubles flared up.

Although this woman's nervousness and marital troubles made her such a poor subject for scientific study that I was never sure of the diagnosis, there were many reasons for believing that the mucous colitis and generalized body pain were due to the absorption of certain substances from the digestive tract, particularly at those times when the feces were soft.

The difficulties of diagnosis are shown also by the case of an intelligent woman, aged fifty-one, who complained principally of lack of energy but somewhat also of sensitiveness to food. As a child she had suffered with urticaria but later outgrew the tendency. She had always been subject to excessive sneezing, as was her father before her. So far as she knew there were no other signs of allergy in her relatives. The bowels moved normally, but the colon was always sensitive. Sometimes laxatives made her feel better but at other times they made her worse. She suspected that milk disagreed with her but she was not sure. She was sure that she could not take cocoa or chocolate. The appendix was removed at the age of eighteen after two attacks of pain. Never afterward was there any abdominal pain. The only symptom of indigestion left was the feeling, at times, that the food remained too long in the stomach. In order to avoid wakefulness from this slight distress she was accustomed to eat a light dinner.

Twenty years before I saw the patient she had suffered a nervous breakdown from over-doing. She was often troubled with irritability of the bladder and frequent urination, and occasionally there were rheumatic pains throughout the body, but these could be accounted for by the presence of definite changes in the joints of the spine. As a girl she had suffered with pain in one hip and had been on crutches for two years.

Although there was little in the history or physical examination to suggest hypothyroidism, besides the constant feeling of fatigue, the metabolic rate was measured and found to be −15, and to my surprise, a daily small dose of thyroid put an end to all her symptoms and made her feel like a new woman. I have not heard from her for several years but I suspect that the sensitiveness to food returned.

Another woman aged sixty-two years taught me most forcibly that pitfalls await the man who would explore the field of intestinal allergy. This woman had always been well and strong and had enjoyed perfect digestion. The only food that she avoided was strawberries, because they produced severe and prolonged attacks of urticaria. She had wheezed for ten or fifteen years, and shortly before coming to see me this symptom had become troublesome. The "asthmatic" attacks had a tendency to come during warm weather but otherwise there was no seasonal influence. Sick headaches occasionally followed unusual nerve strain.

Five months before I saw the patient she ate banana salad and next morning woke with a swollen, itching left hand. Shortly thereafter the face began to itch, and a disfiguring rash appeared about the nose and cheeks. After a week this faded, and for a time, avoidance of salads seemed to insure absence of further attacks. Then another outbreak in the left hand followed the eating of a combination salad. Although these events seemed for a time to prove the etiologic importance of salad, the appearance of fresh outbreaks during the course of a saladless regimen soon showed that the cause was still unknown. To me the most curious feature of the disease was that although the rash came more and more frequently on the left hand, it never involved the right hand, and only occasionally appeared on the face.

When I first saw her she had lost 30 or 40 pounds, and was so weak that she could barely walk. It had been her misfortune to be treated at the same time by a dermatologist who interdicted starches and an internist who, having discovered a mild degree of hypertension, prohibited protein. When I saw her, she was living on little more than a few vegetables. The blood pressure was 170 systolic and 98 diastolic, and wheezy râles could be heard all over the chest.

As there were so many features suggesting sensitiveness to food, I too, for a while was misled. I had her skin tested but she did not respond to any of the proteins applied. Believing that it was better for her to continue living with "eczema" and hypertension than to die of starvation with a clean skin and a normal blood pressure, I gave her sufficient food and protein for the needs of her body, and she promptly regained weight and strength.

The lesions on the skin looked to me like those resulting from a chemical irritant so I asked her to watch for some occupation which would bring into use the left hand and not the right; and it was not long before she found it. She was very fond of primroses, and with the watering pot in the right hand she used the left to pick off dead leaves; occasionally a blossom appeared, and when she smelled it her face broke out. The primroses were given away and that was the end of the skin eruption. The wheezing remained, but that was due to permanent changes in lungs and heart. Primrose poisoning is probably fairly common because, once on the watch for it, I soon recognized several cases.

As I said before, the problem of explaining such cases as have here been described is a difficult one, and one that will, in its solution, demand a broad clinical experience, much self-

criticism, and long-continued observation of the patient. It may well be that hundreds of persons would be cured and perhaps spared needless operations if we could recognize the existence of allergic sensitiveness and then identify the foods at fault. Perhaps it would be helpful to keep in mind that the offending substance is not necessarily a protein. It may often be an irritant oil, a glucosid, an alkaloid, or other potent drug similar to those found in purgative, emetic, and poisonous plants. It may be helpful also to keep in mind that hypersensitiveness to food may be responsible for the production of arthritic pain, mucous colitis, headache, and frequency of urination. What is most needed today is a definite answer to the question: Can one in searching for the cause of vague indigestion exclude allergy or sensitiveness to foods when the patient has never suffered from urticaria, hay-fever, or asthma? If one can, the problem is simplified; if one cannot, then doubtless many cases, easily curable, are going unrecognized.

PAROXYSMAL TACHYCARDIA AND ALTERNATING INCOMPLETE RIGHT AND LEFT BUNDLE-BRANCH BLOCK WITH FIBROSIS OF THE MYOCARDIUM; FAILURE OF THE RIGHT VENTRICLE DUE TO AN ANCIENT THROMBUS IN THE PULMONARY ARTERIES; FIBROMYXOMA OF THE LEFT AURICLE OCCLUDING THE MITRAL ORIFICE AND SIMULATING MITRAL STENOSIS

ARLIE R. BARNES AND WALLACE M. YATER

PAROXYSMAL TACHYCARDIA AND ALTERNATING INCOMPLETE RIGHT AND LEFT BUNDLE-BRANCH BLOCK WITH FIBROSIS OF THE MYOCARDIUM

A WOMAN aged twenty-four years entered the clinic in March, 1926, complaining of dysmenorrhea, palpitation of the heart, and dyspnea. She had had influenza in 1918 and again in 1925, the latter attack being complicated by pleurisy. She had been married four years but had never been pregnant.

A systolic mitral murmur and a slight increase in the transverse diameter of the heart were noted. The electrocardiogram showed a rate of 63, slurred QRS complexes in all derivations, right ventricular preponderance, and inverted T waves in derivations II and III. An indeterminate amount of digitalis had been administered prior to this tracing.

In June, 1927 the patient was again admitted complaining of dysmenorrhea. Her chief concern now was the occurrence of attacks of rapid heart action with dyspnea, cough, and the expectoration of frothy mucus. Definite murmurs were not heard in the heart, although a moderate degree of cardiac enlargement was still present. The blood pressure which had been 108 and 78 at the first admission was now 80 and 60. The examination was negative otherwise and two Wassermann reactions on the blood were negative. The electrocardiogram showed a rate of 69, left ventricular preponderance, exaggerated P waves in derivations I, II, and III, incomplete bundle-branch block with a QRS interval of nine-hundredths to sixteen-hundredths second and an inverted T wave in derivation I (Figs. 253, 254). Two subsequent tracings taken two and seven days later respectively were essentially the same except for variations in the width of the QRS complexes up to sixteen-hundredths second. While the patient was under observation in the hospital an attack of tachycardia developed with a rate of 200 with dyspnea

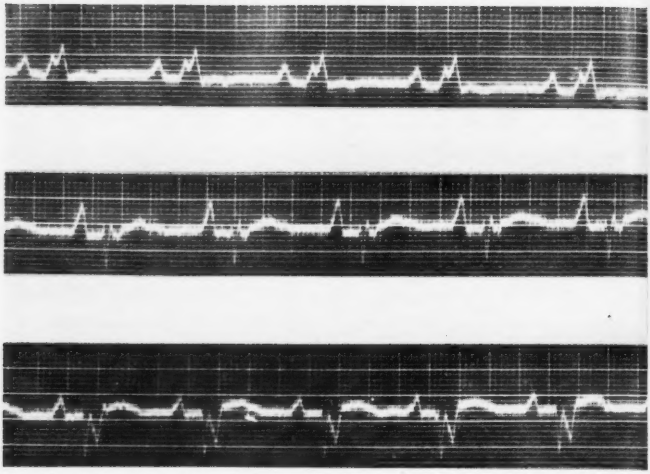

Fig. 253.—Rate 69. Left ventricular preponderance; incomplete right bundle-branch block; QRS interval sixteen-hundredths second in derivations I and II, nine-hundredths second in derivation II; exaggerated P wave in derivations I, II, and III; T wave negative in derivation I.

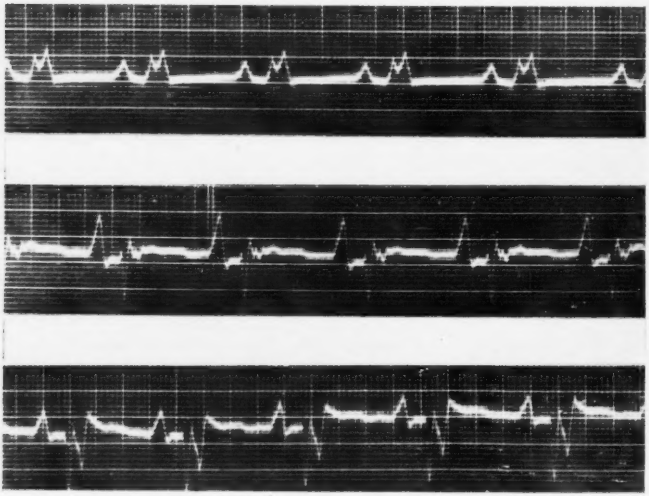

Fig. 254.—Rate 63. Left ventricular preponderance; incomplete bundle-branch block; QRS interval sixteen-hundredths second, exaggerated P wave in derivations II and III.

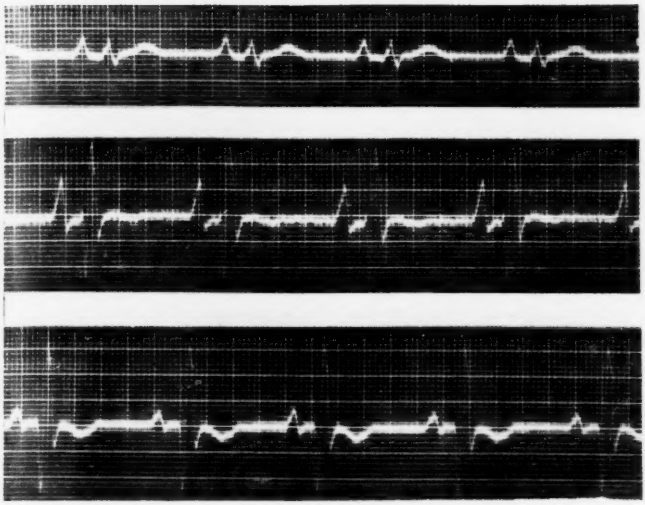

Fig. 255.—Rate 56. Slight right ventricular preponderance; incomplete bundle-branch block; QRS interval twelve-hundredths second, exaggerated P wave in derivation II; T wave negative in derivations II and III.

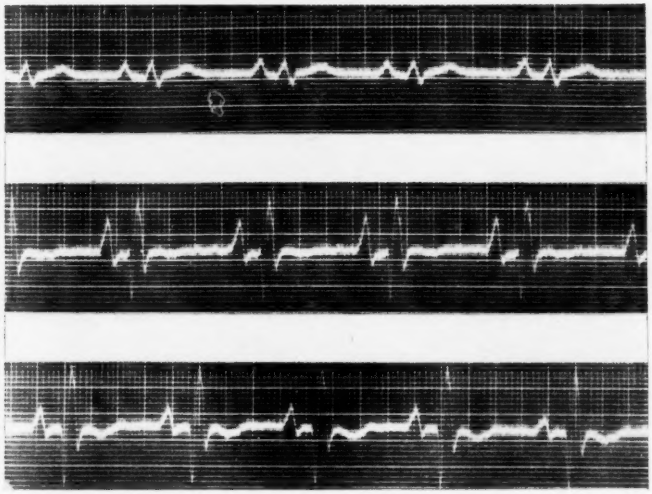

Fig. 256.—Rate 62. Slight right ventricular preponderance; incomplete bundle-branch block; QRS interval twelve-hundredths to sixteen-hundredths second; exaggerated P wave in derivations II and III. T wave negative in derivations II and III.

and the expectoration of 250 c.c. of frothy fluid. This attack stopped before a tracing could be obtained but one taken afterward showed a rate of 56, right ventricular preponderance, exaggerated P wave in derivation II, inverted T waves in derivations II and III, and incomplete bundle-branch block with a QRS width of twelve-hundredths second (Fig. 255). A similar tracing was obtained four days later (Fig. 256) and again twenty-five days later. While the patient was in the hospital under observation for a period of forty-one days she was observed in two attacks of paroxysmal tachycardia with pulmonary edema. The medication consisted of quinidin sulphate, 4 grains,

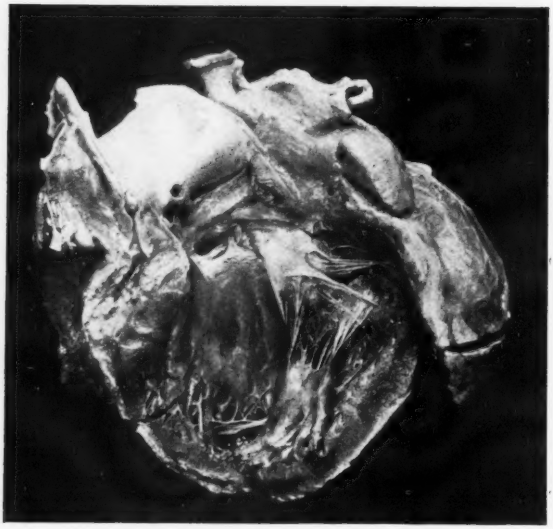

Fig. 257.—(Case 1.) Dilatation of the opened left ventricle; with suggestive fibrosis. The mouth of the aneurysm in the membranous portion of the interventricular septum may be seen. The displaced orifice of the right coronary artery is above it.

three times daily. It was not possible during this period to make a diagnosis of a definite type of cardiac lesion.

In July, 1928 the patient was admitted to the clinic for the third time. Since her former admission and until thirty days before, she had been subject to occasional attacks of tachycardia without symptoms of pulmonary edema. In the last thirty days she had been subject to frequent attacks of tachycardia with dyspnea and the expectoration of much frothy blood-tinged mucus. In some of these attacks there was pain along the left border of the sternum radiating down the inner surface of the left arm. Examination of the heart disclosed a well marked systolic murmur at the aortic area, a faint systolic

murmur at the apex and distant apical tones. The heart was slightly enlarged in its maximal transverse diameter. The blood pressure was 91 and 60. The electrocardiogram taken on admission showed an incomplete bundle-branch block with a QRS interval varying from fourteen-hundredths to sixteen-hundredths second, a P-R interval of twenty-four-hundredths second, and right ventricular preponderance. A tracing taken during an attack of pulmonary edema gave similar data and, in addition, exaggeration of the P waves in all derivations and inversion of the T waves in derivations II and III. The patient was in the sixth month of pregnancy, and was having attacks of pulmonary edema without attacks of paroxysmal tachycardia. Death resulted from an unusually severe attack of pulmonary edema seven days after the last admission.

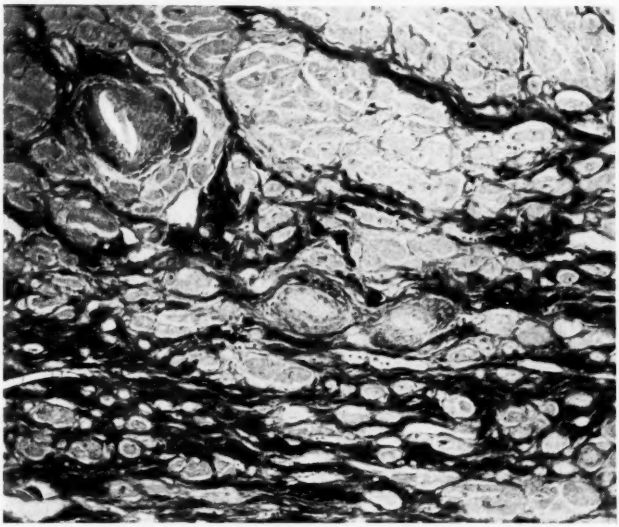

Fig. 258.—(Case 1.) Section from the left ventricle. The dark portions indicate the fibrous tissue (van Gieson's stain), and the light areas the muscle fibers. Three large arterioles are shown with their thickened walls (× 80).

At necropsy the lungs, liver, and spleen showed evidence of passive congestion. The heart was globular with a rounded apex. There was only moderate hypertrophy (375 gm.), more evident in the right ventricle than in the left. The left ventricle was considerably dilated but the right ventricle only slightly so. The epicardium and valves appeared normal and the coronary arteries were not sclerotic. The two outstanding features were marked fibrosis of the myocardium of both ventricles and an aneurysmal pouch in the membranous portion of the interventricular septum (Fig. 257).

The fibrosis of the myocardium was manifested by white streaking, which was extensive in both ventricles but more prominent in the left. The aneurysmal pouch was a thin, membranous, multilocular sac in the membranous portion of the interventricular septum beneath the aortic valve and at the point of juncture of the aortic cusp, above which the right coronary artery takes origin, and the cusp which is not below the origin of either artery. Its orifice was about 0.8 cm. in diameter and opened into the left ventricle; the sac was about 0.8 cm. deep and projected into the right auricle between the septal and anterior cusps of the tricuspid valve. The orifice of the right coronary artery was displaced upward and toward the point of juncture of the same two cusps of the aortic valve to which reference has just been made.

Blocks of tissue were removed for histologic examination from various parts of the ventricles and auricles. Blocks were also removed which included the sino-auricular node, the auriculoventricular node, the bundle of His, the origins of the bundle-branches and the aneurysmal sac. The latter blocks were sectioned serially and every fifteenth section was mounted and stained with hematoxylin and eosin, and every sixteenth section was mounted and stained with van Gieson's preparation. The sections of the left ventricle showed extensive increase in the fibrous connective tissue, in the form of dense fibrous trabeculæ running in the direction of the muscle fibers and often surrounding individual muscle fibers. The larger arterioles had thickened walls due mostly to an increase in thickness of the muscular coat without much if any constriction of the lumen of the vessels (Fig. 258). The muscle fibers appeared normal and without fatty degeneration. The sections of the right ventricle showed similar but less severe fibrosis and the arterioles were not appreciably thickened. Inflammatory cells were not seen in any of the sections. The auricles were quite free from fibrosis. The sections of the sino-auricular node showed that important structure to be normal in all respects. The auriculoventricular node, the bundle of His and the origins of the bundle-branches also appeared normal, except for considerable venous engorgement. The bundle of His was not distorted by the aneurysmal sac; it passed through the thin membranous portion of the interventricular septum below and lateral to the sac. The aneurysmal sac was seen to have a thin fibrous wall and was multilocular. It appeared to be a developmental defect of the membranous portion of the interventricular septum. Sections from both sides of the muscular portion of the interventricular septum revealed normal Purkinje fibers of the left branch on the left side, but the right bundle-branch could not be recognized on the right side. The muscle of the interventricular septum was just as fibrotic as that of the walls of the ventricles. Microscopic sections of the lungs, liver, spleen, and kidneys showed acute passive congestion.

It was difficult to explain the alarming manifestations in this case attending the attacks of paroxysmal tachycardia in view of the paucity of evidence of organic disease of the heart. In a previous study[6] it was observed that a good prognosis at-

tended paroxysmal tachycardia provided a serious underlying disease of the heart was not present. Necropsy revealedt he cause of the serious disease of the heart in the fibrous myocarditis affecting both ventricles but predominantly the left.

The occurrence of severe pulmonary edema in this case with preponderant injury of the left ventricle is in accord with the view that pulmonary edema is due to imbalance between the right and left ventricle in which the left ventricle suddenly becomes unable to maintain an output equal to that of the right ventricle.

Fibrosis of the myocardium of the extent observed here is seldom seen except in cases of marked sclerosis of the coronary arteries. Inasmuch as the coronary vessels in this case were approximately normal it seemed that a previous infection of the heart muscle with subsequent fibrosis was the probable mechanism.

Electrocardiographic changes which were unique in our experience occurred in this case. At the second admission the tracings showed incomplete bundle-branch block with left ventricular preponderance and inversion of the T wave in derivation I. Except for the low amplitude of the QRS complex this tracing might be classified as complete right bundle-branch block. Following an attack of paroxysmal tachycardia the electrocardiogram suddenly shifted to incomplete bundle-branch block with right ventricular preponderance and inversion of the T waves in derivations II and III. Except for minor details this tracing would be classified as complete left bundle-branch block. This suggests that the bundle branches were alternately involved either functionally or organically. However, serial sections of the main stem of the left bundle-branch did not show any significant lesion. It was not possible to follow the main stem of the right bundle-branch either because of the inherent difficulty normally encountered in identifying it or possibly because it was obscured or replaced by the fibrous changes in the right ventricle.

This is one of a very few cases of paroxysmal tachycardia in which a careful histologic study of the heart has been made.

Vaquez, Cade and Rebattu, Falconer and Duncan, Falconer and Dean, and Butterfield and Hunt all found lesions, either in the sino-auricular node or in some part of the conduction system as well as in the myocardium. These changes were not constant enough, however, to account for the arrhythmia, and in another case studied by one of us (Yater) cardiac lesions were not revealed. In the present instance from a histologic standpoint there is nothing to account for the attacks of paroxysmal tachycardia.

FAILURE OF THE RIGHT VENTRICLE DUE TO ANCIENT THROMBUS IN THE PULMONARY ARTERIES

A man aged thirty-four years came to the clinic in August, 1926 complaining of difficulty in swallowing, daily vomiting after breakfast and marked dyspnea on exertion. Fifteen months previously septicemia had followed an infection of the hand and he had not recovered satisfactorily. He was troubled with pains in the joints and severe cramps in the muscles of the legs. Four months before admission a sudden attack of pain in the left side of the chest had occurred. This pain was made worse by breathing. About a week later similar pain occurred in the right side of the chest following which the patient became very short of breath. He improved gradually and was able to go back to work.

Examination did not disclose a satisfactory explanation of the patient's complaints. The only significant finding was a positive blood Wassermann reaction. A course of antisyphilitic treatment was carried out while the patient was under observation. About two months later the patient complained of a recent exacerbation of the shortness of breath with a dry cough, daily chill, anorexia, and weakness. At this time the roentgenograms and the symptoms were indicative of abscess of the lung. Spirilla and fusiform bacilli were found in the sputum and in view of this and of the findings indicative of syphilis, salvarsan was again administered. In three weeks there was marked improvement; evidence of abscess of the lung was no longer present. However, the patient remained dyspneic; the heart was definitely enlarged and it became apparent that the chief trouble was due to myocardial insufficiency. The electrocardiogram at this time showed a rate of 112, right ventricular preponderance and inverted T waves in derivations II and III.

The patient was reëxamined in March and October, 1927, March, 1928, and finally in September, 1928. The essential observations at all of these visits were: evidence of congestive heart failure, marked cardiac hypertrophy, gallop rhythm at the apex, marked accentuation of the second pulmonic sound, and electrocardiographic data similar to those described. The patient gradually became more dyspneic and edematous and during the later stages of his illness erythrocytosis and a hemoglobin of 110 per cent by the acid hematin method developed. Death occurred from progressive myocardial failure.

The significant features of this case are revealed by the pathologic anatomic diagnosis: (1) Ancient (two-year) thrombosis of the pulmonary arteries (embolism?); (2) hypertrophy of the heart (470 gm.), especially of the right ventricle, with dilatation, graded 3, and fatty changes, graded 2; (3) vegetative mitral endocarditis (rheumatic?); (4) bronchiectasis with abscess formation in the base of the right upper lobe; (5) bilateral chronic adhesive pleuritis, and pericarditis; (6) edema, graded 3, of scrotum, legs, and arms and (7) bilateral hydrothorax. The striking and significant features were the old thrombi in the main trunk of both pulmonary arteries, and the hypertrophy of the right ventricle. The thrombi were dense white masses about 4 cm,

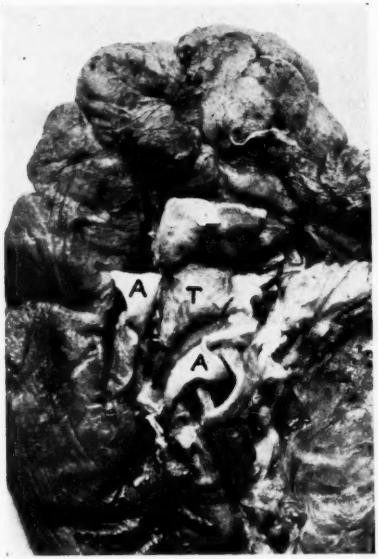

Fig. 259.—(Case 2.) The right pulmonary artery has been opened. *A*, *A*, indicate the portions of the wall of the artery on each side of the adherent thrombus, *T*.

long and 0.5 to 1 cm. in diameter, in the pulmonary arteries between the main pulmonary trunk and the subdivision of the arteries into their branches (Fig. 259). These thrombi greatly reduced the lumen of the pulmonary arteries, the right more than the left. They were firmly adherent to the walls of the arteries. The hypertrophy of the heart was entirely of the right side; the average thickness of the wall of the right ventricle was 0.6 cm. (normal 0.3 cm.). The orifice of the pulmonary artery was dilated and measured 10 cm. (normal 7.5 cm.). The coronary arteries were not appreciably sclerotic and seemed to be dilated. The myocardium was grossly normal, but there

was a suggestion of fatty degeneration. The endocardium and valves were apparently normal except for the mitral valve, on which was a patch of firm "dewdrop" verrucæ, appearing to be of rheumatic type rather than of subacute bacterial type. The pericarditis was of no great moment, but the pleuropericardial adhesions had distorted the cardiac shadow on the left side. The lungs grossly showed little evidence of disease except for an abscess communicating with a bronchus in the base of the right upper lobe. The color of the parenchyma of the lung near the hilum suggested the presence of hemosiderin. There were pleural adhesions on both sides of the thorax and between the lobes of the lungs. Numerous subpleural petechiæ were present.

The thrombi in the pulmonary arteries were not organized. Intimately adherent to the wall of the artery was a layer of dense, hyaline material and outside of this was a large mass of fibrin with some red blood cells in the interstices of the half of this layer nearest the lumen of the artery. The wall of the pulmonary artery did not show evidence of inflammation. From this picture alone one could not determine the age of the thrombus, but it might be called old because of the hyalinization of the deeper portion. The parenchyma of the lungs showed evidence of previous disturbance in various areas in a hyaline thickening of the walls of the smaller arteries and sometimes even organization of old thrombi. In the region of the abscess in the right upper lobe there was definite evidence of an ancient infarct. The presence of the hemosiderin was confirmed; it was contained within phagocytes in the alveoli. The muscle of the heart did not show anything of note except fatty degeneration. The mitral vegetation proved to be a non-inflammatory mass of hyaline material and was, therefore, probably a rheumatic lesion. The liver and spleen showed chronic passive congestion.

This case presented unusual problems in diagnosis as it was difficult to find a satisfactory explanation for the serious myocardial failure. Murmurs were not heard on which a diagnosis of valvular disease could be made. There was no evidence of hypertension and no history indicative of coronary disease. If syphilis were a factor in the heart failure, we would expect to find it manifested in some form of aortic disease, as syphilis of the myocardium occurs rarely if at all. The marked accentuation of the second pulmonic sound and the electrocardiogram in which the T waves were inverted in leads II and III, an inversion commonly associated in our experience with strain on the right side of the heart, led to a diagnosis of chronic myocardial failure chiefly of the right ventricle and due to some obstruction to the pulmonary circulation, either intrapulmonic or in the form of unrecognized mitral stenosis. In view of the necropsy data it

is apparent that we did not give sufficient weight to the history of two severe seizures of pain in the right and left sides of the chest followed by severe dyspnea. These seizures undoubtedly signalized the occurrence of pulmonary emboli and furnished an explanation for the thrombi found in the pulmonary arteries at necropsy. The obstruction to the pulmonary circulation accounts for the failure of the right ventricle.

This case raises the question of whether actual pulmonary hypertension occurs. Yater and Constam have discussed this in another article in this volume. In their cases the increased resistance was thought to be due to pulmonary arteriosclerosis, producing a condition analogous to essential hypertension of the systemic circulation. In the present instance, although the clinical features were in many ways identical to their first case, the increased resistance was produced by obstruction of the main pulmonary arteries, that is, central to the arterioles.

This case illustrates well a fact that we are likely to forget, namely, that obstruction to the pulmonary circulation of various types, a rare example of which we see here, places a severe strain on the right ventricle and eventually brings about myocardial failure.

FIBROMYXOMA OF THE LEFT AURICLE OCCLUDING THE MITRAL ORIFICE AND SIMULATING MITRAL STENOSIS

A woman aged twenty-three years came to the clinic June 16, 1927 complaining of shortness of breath, palpitation of the heart and weakness for a period of two years. The onset of symptoms had not been acute or definite; they had become distinctly worse in the last six months with some swelling of the ankles and feet at the end of the day. Nausea, vomiting, and gaseous distention in the epigastrium constituted the chief complaint on admission. The previous history was not significant.

Examination of the heart showed a presystolic murmur and thrill at the apex and a systolic apical murmur transmitted to the axilla. The second pulmonic sound was markedly accentuated. There was moderate cyanosis of the lips and nails. The laboratory data were not significant except that a teleoroentgenogram showed evidence of definite cardiac enlargement. The electrocardiogram showed a rate of 80, a notched QRS wave in derivation III, notched P wave in derivations I, II, and III, an inverted T wave in derivation III and left ventricular preponderance.

The patient's response to the administration of digitalis and to every effort at treatment was not satisfactory and her course was progressively downward. She died from cardiac failure twenty-nine days after admission.

The usual conditions of chronic passive congestion of the liver and spleen, ascites and hydrothorax, and pulmonary infarcts were found. The heart weighed 374 gm. In the left auricle, attached by a broad base to the interauricular septum in the region of the fossa ovalis, was an elongated, irregularly round, gelatinous looking tumor which measured 6 by 4.5 by 3.5 cm. (Fig. 260). It practically filled the auricle and its lower fourth almost occluded the mitral orifice. On the surface of the tumor were a few small areas of hemorrhage; when the mass was bisected the cut surface resembled colloid material and was very hemorrhagic. The ventricles were both markedly dilated, particularly the right, and the walls of the latter chamber were considerably hypertrophied. The valves appeared normal except for small terminal vegetations on the tricuspid. The coronary arteries were smooth.

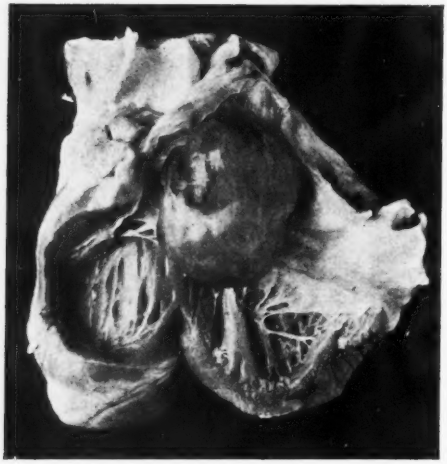

Fig. 260.—(Case 3.) The left auricle and ventricle have been opened, revealing the fibromyxoma attached to the wall of the auricle.

Microscopic study verified the suspected chronic passive congestion of the various viscera and the infarcts of the lungs. The tumor of the heart was found to be a fibromyxoma with areas of hemorrhage in its substance.

The data in this case were those seen in classical mitral stenosis. The patient's gradual progressive failure over a period of two years, the lack of recovery from previous decompensations and the failure to respond to the usual methods of treatment, aroused our suspicion that we were not dealing with an ordinary case of mitral stenosis. The tumor encountered is perhaps the

most common type of tumor of the heart; it is usually situated in the left auricle and is attached to the interauricular septum. Its simulation of rheumatic mitral stenosis by prolapse into the mitral orifice was most unusual. A similar tumor was found in another case but the growth, although as large as this one, had remained entirely in the left auricle. The patient, in this case, a woman aged about forty years, had had some dyspnea on effort for two years but examination of the heart was always negative. She died of septicemia following abortion.

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UNUSUAL CASES OF THROMBO-ANGIITIS OBLITERANS: THEIR ASSOCIATION WITH POLYCYTHEMIA VERA AND TRAUMATIC MYELITIS

BAYARD T. HORTON AND GEORGE E. BROWN

THE typical cases of thrombo-angiitis obliterans may easily be diagnosed if one has in mind a simple working classification of peripheral vascular diseases. The atypical case, however, frequently offers difficulties in diagnosis, especially if it is associated with some other clinical syndrome.

THROMBO-ANGIITIS OBLITERANS ASSOCIATED WITH POLYCYTHEMIA VERA

Case 1.—A man aged fifty-five years, a druggist, came to the clinic November 27, 1928, because of gangrene in the right great toe, which had been present for three weeks. His general health had been good up to the onset of the present illness. For the last six or seven years he had occasionally noted sharp, stinging pain in the arch of the right foot, which seemed to be associated with exercise. In July, 1928, he began to have a series of painful varicose ulcers on the inner aspect of the right leg; about nine ulcers occurred, each healing in three or four weeks. Swelling of the ankle or sharp pain did not occur before the onset, and the ulcers did not bleed. In August a rather sudden severe pain occurred in the right great toe which persisted until about a week before admission when the nail came off. The toe was blue for several weeks after the onset of pain and about September 15 it became black around the edge of the nail; this area gradually spread so that for the last week or ten days the entire distal half of the foot was deep blue. The color in the face had been of a reddish hue for the last five or six years, especially around the nose and cheeks, but the lips had been red for only approximately six or eight months. About a month before, he had experienced a dull pain in the left upper quadrant and it was discovered that his spleen was enlarged. The pain lasted only a few hours. Since September he has noted that his lips were dark red.

The patient appeared to be about sixty-five years of age, although he gave his age as fifty-five. The systolic blood pressure was 130 and the diastolic 86. There were numerous telangiectatic areas on the nose, an eruption of the skin (acne rosacea) of the forehead, and a brownish pigmentation of the face, the latter following ultraviolet treatment. The sclerotics on the nasal

side and the conjunctiva were acutely injected. The tongue seemed fairly normal in color, but the lips were dark red and cyanotic. The whole body was tanned by violet rays. The remainder of the general examination was essentially negative, except for splenomegaly and the condition of the extremities. The spleen measured 11 cm. below the costal margin in the median clavicular line. It felt hard. The edge of the liver was not palpable. There was a brownish pigmentation over the lower half of the right leg with many thrombosed veins and scars over this area which had been present for four months. The same brownish pigmentation was present over the left foot, but to a less degree. There was definite gangrene of the right great toe with cyanosis of the foot, graded 4. The pulsation in the right femoral artery seemed practically normal, but pulsation could not be felt below that point. The vessels in the hands and all vessels in the left leg pulsated normally except the dorsalis pedis; it pulsated intermittently. The circulatory test disclosed marked pallor of the right foot when it was elevated to 180 degrees and marked cyanosis with rubor when it was dependent. The palpable vessels including the brachials seemed soft; sclerosis was not demonstrable. Laboratory tests, including roentgenograms of the vessels of the extremities, were negative, except for the blood picture. On admission the acid hematin was 18.7 mg. per cent (normal 14.5), erythrocytes numbered 5,250,000, and leukocytes 18,100; the blood urea was 43 mg.; creatinin was 1.7 mg., and blood sugar 0.94 per cent. The Wassermann test of the blood was negative. The phenolsulphonephthalein return was 75 per cent in two hours. The viscosity was 10 (normal 4.5) and the total blood volume was 8,260 c.c. or 131 c.c. for each kilogram of body weight (normal 87.5 c.c. for each kilogram of body weight). November 29, December 1, and December 3, venesection was performed and 500 c.c. of blood, 400 c.c., and 400 c.c. respectively was withdrawn. Following the venesection the sclerotics, conjunctivæ and face became normal in color; the brick-red color disappeared from the lips, the erythrocytes numbered 4,760,000 and the hemoglobin was 80 per cent (Dare).

The right leg was amputated above the knee December 6. The patient recovered uneventfully. In the amputated specimen the popliteal artery was completely occluded at the site of amputation by an ancient canalized thrombus. The thrombus extended down into the tibial vessels. Below this level, the occlusive process was patchy in its distribution, with areas of occlusion, followed by segments in which the vessels appeared normal. The distribution of the occlusive process was typical of that seen in thrombo-angiitis obliterans, instead of arteriosclerosis. The calcification in the vessels was not any more marked than one would expect to find in a man of his age. The microscopic sections taken at various levels of the arterial tree were typical of the picture seen in thrombo-angiitis obliterans, and justify that diagnosis.

This is an unusual case in many respects and is the first we have seen in which thrombo-angiitis obliterans was associated with polycythemia vera. Thrombo-angiitis obliterans, as a rule, affects men between the ages of twenty-five and forty-five years;

it is seldom seen in persons more than fifty years, as most of these belong in the arteriosclerotic group. The enlarged spleen and the high viscosity, associated with increased blood volume (131 c.c. for each kilogram of body weight), make the diagnosis of polycythemia vera certain. On account of the patient's age and the presence of the thrombo-angiitis obliterans, it did not seem wise to use phenylhydrazin hydrochlorid to promote destruction of blood, and venesection was, therefore, resorted to with satisfactory results. Venous thrombosis frequently occurs in cases of polycythemia vera, and it is not possible to determine the part it played in this case in the gangrene of the right foot. However, it seems reasonable to assume that thrombosis would take place more readily in a case of thrombo-angiitis obliterans associated with increased viscosity and blood volume, than in a similar case in which viscosity of the blood and the volume of blood were normal. This was borne out by the fact that the patient had thrombosis of several of the superficial veins in the left arm following venesection. The sudden pain in the splenic region, with residual tenderness, was probably due to a splenic infarct, as this is not uncommon in cases of polycythemia vera. The polycythemia vera will probably be controlled by the removal of 500 c.c. of blood, every six to eight weeks. A protective regimen for the extremities was outlined, which we feel will be adequate in this case.

THROMBO-ANGIITIS OBLITERANS ASSOCIATED WITH RESIDUAL TRAUMATIC MYELITIS, FOLLOWING FRACTURE OF THE FIRST LUMBAR VERTEBRA

Case 2.—A man aged forty-three years of Irish and Dutch descent, came to the clinic August 8, 1928 because of pain in the left leg, when he walked. He had used tobacco for twenty years; he usually smoked a pipe, but frequently smoked from four to six cigarettes daily. February 18, 1925, he had been in an automobile accident and sustained a fracture of the first lumbar vertebra with complete paralysis of the entire body below that level, including control of the urinary bladder and rectum. He was unable to move the legs for a period of ten days, but did not believe any sensory disturbances were present. The spine was immobilized by means of a plaster-of-Paris cast for six weeks, and three weeks after the cast was removed the patient was able to walk. Four months after the accident he appeared to walk normally. He gradually regained control of the bladder and rectum

so that in five or six months the voluntary control seemed almost normal. However, he had continued to notice slight soiling of the underwear, both from feces and urine. He had continued at his routine clerical work and had good health until June 1, 1928, when on a camping trip in the mountains while walking at an altitude of 5,000 feet he suddenly experienced severe pain in the calf of the left leg. The foot and leg were waxy white. With rest the pain became less severe and he was able to hobble a distance of a fourth of a mile to the camp. Warm water was used to bathe the leg, which gave some relief, and the pain disappeared in two or three hours. Since that time he had had intermittent calf claudication in the left leg, always associated with exercise and relieved by rest. Walking one to two blocks, at the time of admission, produced pain in the left leg. There was no history of superficial phlebitis.

On examination the patient appeared well developed, well nourished, and healthy. The general examination was essentially negative, except for a slight kyphotic deformity at the level of the first lumbar vertebra, and the condition of the extremities. There was slight atrophy of the muscles in the calf of the left leg, and the left foot felt colder than the right. Both radial arteries pulsated normally, but there was definite diminution in the pulsations of the ulnar arteries. The pulsations in the right leg seemed normal, except in the popliteal artery in which pulsation was diminished about 50 per cent. On the left side the femoral artery pulsated normally, but pulsations could not be felt below that level. The circulatory test revealed rubor, graded 2, with the left foot in the dependent position, and blanching, graded 2, with the foot elevated. The circulation in the hands and right leg seemed normal. A roentgenogram of the teeth revealed one tooth to be infected. Septic tonsils and severe nonspecific infection of the prostate were noted. The neurologic examination was not significant. The various laboratory tests were negative except for the roentgenogram of the spine, which showed old fracture of the first lumbar vertebra. A diagnosis of thrombo-angiitis obliterans, with residual traumatic myelitis, was made.

Two intravenous injections of triple typhoid vaccine were given with a satisfactory reaction each time. Contrast baths and postural exercises for the feet were also given. At the time of the patient's dismissal, after eight days of treatment, he was able to walk more than six blocks without pain.

This case represents an interesting combination of thrombo-angiitis obliterans and residual traumatic myelitis, following fracture of the first lumbar vertebra. The history of intermittent claudication in the left leg, the partial closure of both the ulnar and the right popliteal arteries, together with the other abnormalities in the extremities, make the diagnosis of thrombo-angiitis obliterans certain. There did not seem to be any definite relationship between the injury to the spine and the occlusive peripheral vascular disease, and treatment did not seem

necessary either from the neurologic or orthopedic standpoints. The onset of the sudden pain in the left leg as the initial symptom in a case of thrombo-angiitis is somewhat unusual, but occasionally similar cases are seen. Most patients, however, when questioned closely, give a history of fatigue symptoms in one extremity or more, which they had forgotten. The sudden pain may be due to sudden thrombosis of one of the larger vessels in situ or, more often, to spasm involving one or more of the main arteries. We know that such spasms do occur since we have noted what seemed to be normally pulsating vessels disappear during palpation. Similar spasms have been observed at the operating table, when the vessel was exposed to view.

AMPUTATION OF THE LEFT HAND; SEVERE PAIN IN ALL EXTREMITIES WITH PROMPT RELIEF FOLLOWING ONE FOREIGN PROTEIN INJECTION

Case 3.—An Irishman aged thirty years a cook in the United States Army, registered at the clinic May 28, 1928, complaining of severe pain in all four extremities, which had been present almost continuously for a period of eight months. He had smoked from five to ten cigarettes daily for the last fifteen years. His present illness began in the spring of 1917, at which time his hands and feet felt unusually cold, and when warmed they tingled. Color changes were not observed. This continued at irregular intervals, but was more marked in the winter months. In the winter of 1923 he fainted several times while standing in ranks. He said that he fainted from cold. A painful trophic ulcer developed on the dorsum of the left foot which healed in three weeks. He continued to suffer with cold hands and cold feet until eighteen months prior to admission, at which time he began to have sharp pain in the index and fourth fingers of the left hand. One month later severe pain started in the second left toe; this was followed by severe pain in all the toes of the left foot, except the first toe. He described the left foot as white and dead looking at that time. The pain continued in the left hand at irregular intervals, followed by trophic changes. In October, 1927, the left index and fourth fingers turned black; they were amputated October 24. The wound failed to heal and three weeks later pain developed in the ulcerating stumps. The gangrene gradually involved the hand, and in December amputation of the left hand above the wrist was necessary. This wound healed in two weeks. A painful trophic ulcer which had appeared on the second toe of the left foot in November healed in six weeks. A trophic lesion also appeared in the right thumb at this time and was still present at the time of admission. Bilateral calf claudication had been present for eighteen months, and came on with walking two blocks. The rest pain in the feet seemed to be worse at night, whereas the pain in the upper extremities seemed worse during the day. He had been treated for Raynaud's disease until

December, when the left hand was amputated. At that time a diagnosis of Buerger's disease was made.

On examination the patient appeared undernourished and anemic. He was having considerable pain in the right hand, in the stump of the left forearm and in both feet. He said that he had not been able to sleep comfortably for eight months. There was no history of superficial phlebitis. General examination disclosed marked pyorrhea, one infected tooth, and the condition in the extremities. The stump above the left wrist joint looked normal. There was a small trophic ulcer on the tip of the right thumb, from which pus could be expressed. There was 75 per cent diminution in the pulsation of the right radial and left posterior tibial arteries. The right ulnar, right femoral, right popliteal, left brachial, left femoral, and left popliteal arteries pulsated normally. The right and left dorsalis pedis and the right posterior tibial arteries pulsated intermittently. The circulatory efficiency test seemed normal, except for slight rubor on the dorsum of the left foot when in the dependent position. Otherwise the circulation in the extremities seemed normal. The vasomotor index was 3.5 in the right foot, and 3.3 in the left foot. The systolic blood pressure was 130 and the diastolic 85; the pulse was 80 and the temperature was 98. Analysis of the urine and the blood Wassermann tests were negative. The erythrocytes numbered 4,640,000 and the leukocytes 11,500; the hemoglobin was 85 per cent (Dare). The blood urea was 23 mg. for each 100 c.c., blood sugar was 0.88 per cent, and the phenolsulphonephthalein return was 55 per cent in two hours. Roentgenograms of the legs, arms, and right hand were all negative. A diagnosis of thrombo-angiitis obliterans was made and an intravenous injection of triple typhoid vaccine (100,000,000 organisms) was given. Following this the mouth temperature rose to 101.5° F. and the pain in the extremities entirely disappeared within a period of two to three hours. The patient was entirely free from pain during the rest of his stay in the hospital. His appetite improved markedly; he gained weight and slept well. He remained in the hospital twenty-three days and during that time received five injections, besides the routine treatment of radiant heat, postural exercises and contrast baths. The trophicl esion on the right thumb healed within ten days after admission.

This was a most remarkable case and represents the only one we have seen in which the patient was suffering pain in all four extremities at the time of admission. The relief of the pain which had been present for months, two to three hours after the injection of the typhoid vaccine, was indeed spectacular. We believe that typhoid vaccine given intravenously is a very important agent in the treatment of thrombo-angiitis obliterans; its efficiency is well demonstrated in this case. We have seen similar results in numerous other cases. This is the first case in which it seemed to us that amputation of a hand was necessary.

We have occasionally had to amputate fingers. This type of case is frequently confused with Raynaud's disease.

THROMBO-ANGIITIS OBLITERANS IN THREE MEMBERS OF THE SAME FAMILY

Case 4.—A day laborer aged thirty-three years of German parentage came to the clinic July 9, 1923 complaining of "bad feet" of three years' duration. The family history was negative. Three years before admission, during the winter months, he noticed that both great toes became blue and cold, and he had difficulty in keeping the feet warm even when he wore woolen stockings and heavy overshoes. Six to eight months later he had bilateral calf claudication after walking three to four blocks. January 15, 1922 he had accidentally scratched the left great toe, but not sufficiently to produce bleeding. Three days later an open sore developed, which refused to heal. Rest pain continued up to the time of admission. The ulcer was excised in September, 1922, but the lesion remained open. It was curetted in February, 1923. March 28 perivascular neurectomy of the left femoral artery after the method of Leriche was done. Amputation of the left great toe at the second joint was necessary one month later.

The blood pressure was 128 and 80. The left great toe had been amputated, and a moist discharging ulcer occupied the center of the stump. All peripheral vessels pulsated normally, except the right radial and both dorsalis pedis arteries. Pulsations in these vessels were markedly diminished. Both feet showed rubor, graded 2, in the dependent position, and blanching, graded 2, with the feet elevated. The routine laboratory tests, which included that of the urine and blood, blood Wassermann reaction, and roentgenograms of the left leg, were all negative. The diagnosis was thrombo-angiitis obliterans.

The patient was treated medically with nitrites, hot and cold baths for the feet and intravenous sodium citrate injections (250 c.c. of a 2 per cent solution once a week), without any marked improvement in the condition of the extremities. He was dismissed from observation July 28, 1923, and continued the same treatment at home, but without improvement. He was again under our observation for a week in September, 1923, and presented the same physical characteristics as were observed during the previous July. Amputation was advised, but refused by the patient. The open lesion on the left foot continued to persist, and rest pain gradually became so severe that October 6, 1924 the left leg was amputated (elsewhere) 15 cm. below the knee. The stump did not heal, and a few months later a second amputation just below the knee was necessary. The latter required one year to heal.

Case 5.—A cabinet maker aged thirty-four years of German parentage came to the clinic October 15, 1928, complaining of pain in the left foot of three months' duration. The patient had diagnosed thrombo-angiitis obliterans in his own case as the symptoms were so similar to those of his brother (Case 4). He had been a moderate pipe smoker since the age of sixteen years. The tonsils had been cleanly removed ten years before admission. About

three months before admission he had noticed an irritation of the left fourth toe which he attributed to the rubbing of his shoe. A few days later, the third toe was similarly affected. The ball of the foot then became sore. These symptoms persisted up to the time of admission. One year before, for a period of three weeks, similar pain had occurred in the ball of the left foot, for which arch supports were worn without relief. For the last two years he had had recurring superficial phlebitis along the left leg, which would persist for about a week and then disappear.

The patient was well developed and well nourished. He weighed 144 pounds and his height and build were normal. Systolic blood pressure was 136 and diastolic 84. The superficial cord along the medial aspect of the upper third of the left leg was inflamed and could be rolled under the palpating fingers. Biopsy from this area revealed an acutely thrombosed vein, the microscopic sections of which were typical of thrombo-angiitis obliterans. The third and fourth toes on the left foot were reddish and cyanotic in the dependent position. They were markedly pale when elevated. Pulsation could not be felt in the right ulnar or the right and left dorsalis pedis arteries. The pulsation in the left ulnar artery was markedly diminished but the other peripheral arteries pulsated normally. Foci of infection were not found. All of the routine laboratory tests were also negative. A diagnosis of thrombo-angiitis obliterans was made.

The fourth day after admission the patient was given an intravenous injection of triple typhoid vaccine (50,000,000 killed organisms) which produced a satisfactory systemic reaction. More than 90 per cent of the pain and soreness in the left foot disappeared promptly following the vaccine reaction. A second injection was given during his ten-day stay in the hospital, besides the routine treatment. Written instructions with regard to the care of the feet were given him at the time of his dismissal. In addition to the daily use of contrast baths, postural exercises, and radiant heat, we strongly urged the use of intravenous typhoid vaccine, every seven to ten days, for a period of six months, and cessation of all work during this period.

After the patient returned home he compared his feet with those of his brother, aged thirty-eight years, and found that the latter did not have pulsations in the dorsalis pedis arteries. Pulsations in the posterior tibial arteries seemed normal.

Undoubtedly this patient and his brother have thrombo-angiitis obliterans, and it seems probable that a third brother has the same disease in an inactive form. This is the first time we have found the disease in more than one member of the same family. We are not able to make any definite statement as to its significance. The wearing of arch supports without relief in these cases is so common that we occasionally refer to thrombo-angiitis obliterans as the "arch-support disease."

THROMBO-ANGIITIS OBLITERANS OF ALL FOUR EXTREMITIES WITH ACTIVE LESIONS OVER A PERIOD OF THIRTEEN AND A HALF YEARS

Case 6.—A Russian Hebrew aged twenty-seven years first registered at the clinic May 17, 1915 complaining of pain in the right great toe which had been present for six months following the removal of an ingrown toenail.

The general examination was essentially negative except for an ulcer on the inner aspect of the right great toe. A statement was not made with reference to the pulsations in the peripheral arteries. The diagnosis at that time was ulcer of the right great toe, for which local treatment was given. He remained only a few days for treatment. The lesion did not heal and one month later the right great toe was amputated (elsewhere) at the second joint. The wound healed in three months but was very painful; morphin was frequently required for relief.

The patient was well until 1917, except for intermittent claudication in the right leg after walking one block. The stump of the right great toe then broke open, and soreness appeared around the nail of the left great toe. A part of the stump of the right great toe was again amputated and the left great toenail was removed. The latter failed to heal and the toe was amputated at the second joint. Both wounds healed in eight months. The open lesions again became very painful. In 1919 a painful infection occurred around the third left finger and in 1920 a similar infection around the left index-finger. Each lesion required five months to heal. The feet remained well except for bilateral intermittent calf claudication until 1923 (a period of five years) when an infection occurred around the nail of the second right toe. The nail came off and was finally replaced by a new nail. The patient was again free from symptoms except for bilateral intermittent calf claudication until January, 1928 (a period of five years) at which time he began to have numbness and tingling sensations at the base of the right great toe. The stump of the right great toe again broke open, and rest pain was continuous until his second admission May 27, 1928. His complaint at this time was the same as in May, 1915, namely, pain in the right great toe. The home physician had diagnosed Raynaud's disease.

The patient looked tired and worn because of lack of sleep. His weight was 105 pounds. He had lost 30 pounds during the last four months prior to his second admission to the clinic. He had smoked from fifteen to twenty cigarettes daily since he was eighteen. There was no history of superficial phlebitis in the extremities. General examination was essentially negative except for the condition in the extremities. A moist discharging ulcer was present in the stump of the right great toe with the bone protruding in the center of the ulcer. The left great toe had been amputated. The right and left radial and the left femoral arteries pulsated normally. The pulsations in both ulnar arteries were markedly diminished. The right femoral and the right and left posterior tibial pulsations were graded 1, while the left popliteal artery pulsations were graded 3. Pulsations could not be felt in the right popliteal and right and left dorsalis pedis arteries. Both feet were blanched, graded 3, when elevated; rubor, graded 3, of the right foot was present when in the dependent position. The analysis of the urine, blood counts, and tests

of blood sugar and phenolsulphonephthalein were negative. The blood Wassermann reaction was negative and the roentgenograms of the lower extremities were negative for calcified vessels. The patient was treated with radiant heat, postural exercises and the use of intravenous foreign protein killed cultures of typhoid bacilli. Following the first injection of the foreign protein, there was complete relief from pain for a period of six hours. The vascular index was 6.4 in the right foot and 4.3 in the left foot. Because of the relatively high vasomotor index and the relief following the intravenous injection of foreign protein, bilateral lumbar sympathetic ganglionectomy was carried out June 12, 1928 (Adson's technic). For a period of eighteen days following the operation, there was almost complete relief of pain in the right foot. Both feet felt warm and dry and the lesion on the right toe continued to heal, but on the nineteenth day after operation, pain in the right great toe returned. This pain continued, associated with progressive thrombosis around the base of the right great toe, and followed by a further ulceration of the stump of the toe. The right leg was amputated below the right knee August 16, fifty-six days after the lumbar sympathetic ganglionectomy. Healing did not occur and a second amputation was necessary September 13, at which time 3.5 cm. of the stump was removed. Healing again failed to take place and it was necessary to amputate above the knee October 1. Healing occurred promptly following the last operation and the patient was dismissed from observation eighteen days later. Microscopic examination of the amputated specimens disclosed vascular obliteration which we consider typical of thrombo-angiitis obliterans.

This patient is of particular interest from several standpoints. First, his race, age, sex, history, and general clinical data are pathognomonic for thrombo-angiitis obliterans, and yet a period of thirteen and a half years had elapsed without a diagnosis. The fact that the home physician made a diagnosis of Raynaud's disease is still indicative of the fact that the average physician does not yet appreciate the difference between organic and functional diseases of the extremities. It is quite obvious that the patient had thrombo-angiitis obliterans when we first saw him in 1915, but we did not recognize it then. Most of our knowledge with reference to this disease has accumulated since that time. Second, the course of the disease was marked by periods of activity, followed by periods of remission. This is well illustrated with reference to the symptoms in the feet. The period from 1914 to 1917 represents an active period of the disease. This was followed by a five-year period during which the patient was able to carry on his routine work. An open lesion

again appeared on the second right toe in 1923 which healed fairly promptly. Following this, there was a second five-year period of freedom from symptoms, except for bilateral calf claudication, and again the acute symptoms occurred in the right foot, for which amputation was finally necessary. Third, it should be emphasized again that lumbar sympathetic ganglionectomy is not a curative measure in thrombo-angiitis obliterans of the lower extremities as it is in Raynaud's disease. In the former we are dealing with an occlusive vascular process, whereas in the latter we are dealing only with a vasospastic condition which is, so far as we know, entirely functional in origin. In this case, the occlusive process in the right foot was progressive in spite of the increased blood flow to the extremity, following the lumbar ganglionectomy, and not because of it. Most patients with thrombo-angiitis obliterans, and a high vasomotor index do well following this type of operation. Fourth, this case illustrates the difficulty sometimes encountered in obtaining healing following amputation of an extremity. At the present time, we have no accurate clinical method for determining the primary site of amputation. In this case we were anxious to save the knee joint and amputation below the joint was deemed advisable, but later it was necessary to amputate above the joint in order to obtain healing.

DIVERTICULA OF THE COLON AND SIGMOID

PHILIP W. BROWN

THERE is still considerable difference of opinion in regard to the presence and significance of diverticula in the colon and sigmoid. Diverticula are sometimes held responsible for diarrhea, indefinite reflex abdominal symptoms, in fact almost any abdominal complaint. Diverticulitis sometimes produces obstruction; a mass may be palpated in the region of the sigmoid, or urinary symptoms may develop as a result of a fistula. Any of these phenomena may logically suggest carcinoma or a primary condition in the bladder and unless the various possibilities are borne in mind, ill advised surgery, misguided treatment, or an inaccurate prognosis may be perpetrated. It is not always possible, however, to distinguish between carcinoma and diverticulitis of the sigmoid until operation is performed. In 1923 Judd and Pollock reported 118 cases of diverticulitis in which operation was performed and carcinoma was not found, but during the same period operation was performed in nineteen cases of diverticulitis of the sigmoid associated with carcinoma.

The four cases presented here illustrate some of the considerations involved in diagnosis, and the type of treatment.

Case 1.—A man aged fifty-five years came to the clinic because of a dull aching pain in the lower right side of the abdomen which came on at irregular intervals and was relieved by a bowel movement. For the last ten years he had been using cathartics and enemas. Blood was not passed. The appendix had been removed eleven years previously. Other than the fact that the patient was overweight for height and age, the general examination was negative. The urinalysis and blood count were negative. A roentgenogram of the colon revealed multiple diverticula of the transverse and descending colon and of the sigmoid (Fig. 261). A diagnosis of constipation and diverticulosis was made. The patient was advised along lines to correct the constipation.

This is a very clear demonstration of multiple diverticula but other than being of interest from the standpoint of the anatomist, they bear no relationship to the present complaint. The patient obtains relief from his abdominal distress if the bowels move well, and as far as he is concerned that is his chief problem. The correction and prevention of constipation, however, may prove to be of even more value to him. As he grows older, becomes less active, possibly increases in weight, and if the constipation

Fig. 261.—(Case 1.) Diverticulosis of descending and transverse colon without spasm or filling defect.

continues, it is readily conceivable that inflammation may be started in one or more of the diverticula, especially those in the sigmoid where the fecal current is slowest.

Case 2.—A woman, aged forty-seven years, had consulted the clinic on several occasions. The first time was in August, 1923 when her complaint was largely that due to chronic nervous exhaustion and constipation. She had observed that for the preceding four years, the bowel movement was ribbon-shaped. All laboratory data were essentially negative except that the

roentgenogram of the colon revealed multiple diverticula of the rectosigmoid and sigmoid, with which much spasm was associated. A roentgenogram taken five days later showed diverticula filled with barium. The patient was placed on a bland anticonstipation regimen and given tincture of belladonna.

The patient returned to the clinic in March, 1924 and reported having had more or less soreness and distention through the lower part of the abdomen. On two occasions she was confined to bed a few days as the symptoms increased and with them there was a slight fever and unusual difficulty in obtaining a bowel movement. Except for tenderness in the left lower part of the abdomen, general examination was negative. The roentgenogram of

Fig. 262.—(Case 2.) Diverticulitis of sigmoid associated with spasm; occasional diverticula in transverse and descending colon.

the colon was the same as on the previous examination. Medical management was again advised and efforts made to obtain more complete coöperation on the part of the patient in caring for herself.

In September, 1925 the patient was reëxamined; she reported that she had been getting along fairly satisfactorily. There was still some discomfort in the lower part of the abdomen and if constipation began to recur, pains increased and stools were ribbon-shaped. Her weight had remained unchanged and the general examination was negative except for slight tenderness over the sigmoid. Roentgenograms of the colon were the same as noted

previously. She was again dismissed and urged to persevere in keeping her bowels well regulated.

In January, 1927 the patient returned with an increase of former symptoms but without acute attacks of abdominal pain. General examination and roentgenograms (Fig. 262) were the same. In view of the general nervous state and the increased abdominal discomfort the patient was hospitalized and the usual medical measures instituted. While in the hospital acute pain developed in the lower left part of the abdomen which required morphin for relief. A faint trace of bright red blood was noted in one stool. Surgical intervention was considered but after several weeks of medical treatment all symptoms subsided and the bowels were moving satisfactorily.

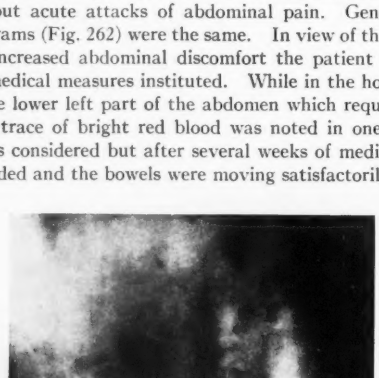

Fig. 263.—(Case 2.) Diverticulitis of sigmoid with filling defect and marked spasm.

In November, 1928 the patient reported to the clinic. She had had one attack of bowel trouble each month. However, for the last three months the trouble had been almost continuous and on several occasions fairly severe pain occurred in the lower left side of the abdomen. Weight had not changed and a mass was not palpable. The blood continued to be normal. The roentgenogram of the colon (Fig. 263) continued to emphasize the marked spasm and an extensive spastic filling defect of the sigmoid which did not disappear after belladonna was given. Proctoscopic examination showed that the sigmoid was immobile and its lumen reduced in size; the mucosa was

thrown into adherent folds and there were points from which pus exuded from invisible sinuses. In view of the progression of symptoms, the marked inflammation and the recent roentgenologic data, operation was advised.

At operation the sigmoid was densely adherent to the surrounding structures and was resected with difficulty. Tube anastomosis was made. Convalescence was satisfactory.

This case illustrates very well the medical treatment of diverticulitis and then the finale when after five years of fairly satisfactory progress, clinical and roentgenographic data were such as strongly to suggest the presence of carcinoma. There is reason to believe that this hard-working farmer's wife had not been able to correct the constipation properly. During her several visits to the clinic, prior to operation, rest and anticonstipation measures seemed to clear up the trouble. Since the attacks of diverticulitis continued to recur, however, more radical measures seemed justifiable in order to effect a cure. Fortunately, the operation did not reveal carcinoma and a satisfactory outcome can be assured.

Case 3.—A man aged fifty-five years seven months prior to his first visit to the clinic, had suffered an attack of pain and soreness in the left lower part of the abdomen. The pain lasted about three days. Associated symptoms were not noted. Four months later, a sudden severe pain developed in the left lower part of the abdomen, with fever up to 100° F. He had had a chill at the onset of the attack. He was unable to obtain a bowel movement. The pain and tenderness persisted for ten days and gradually subsided. It was found that there was obstruction high in the rectum and a diagnosis was made of carcinoma of the rectosigmoid. As soon as he could travel, he started for the clinic and by the time he arrived, six weeks later, there were practically no symptoms except tenderness in the region of the sigmoid. Rectal examination disclosed induration in the region of the rectosigmoid. The urine was normal. The hemoglobin was 79 per cent, erythrocytes numbered 4,820,000, and leukocytes 11,000. The Wassermann reaction on the blood was negative. A roentgenogram of the chest was negative and that of the colon showed multiple diverticula throughout the entire colon (Fig. 264). A diagnosis was made of diverticulitis of the sigmoid with associated diverticulosis of the colon.

The patient was placed on a bland anticonstipation diet and was given mineral oil and intermittent courses of tincture of belladonna. He was reexamined three months later and reported that he had been very well. He wanted to have another roentgenogram of the colon as he was planning an extensive journey; this showed the condition to be about the same although there seems to be less spasm (Fig. 265). The patient returned six months later. He had been very well until three months previously when he suffered

another attack similar to the previous seizures. Ten days after the onset of the attack, marked urinary symptoms developed and fecal matter and blood were passed in the urine. The urinary symptoms subsided in about ten days but had recurred just prior to his arrival in Rochester. General examination revealed a mass in the lower left part of the abdomen which could be felt bimanually; it was rather tender. The proctoscope revealed an extrarectal mass beginning about 12 cm. above the anus. In the urine there was much blood and pus. Because of the urinary symptoms a cystoscopic examination was made and it was found that the whole base of the bladder was covered with bullous edema. The bladder was extremely irritable, with

Fig. 264.—(Case 3.) Diverticulitis of sigmoid with spasm; diverticula in various parts of colon.

resulting small capacity. Fistula could not be demonstrated. In view of the probable vesicosigmoidal fistula and the activity of the condition, a roentgenogram of the colon was not thought to be advisable. The history and present data pointed to diverticulitis with perforation into the bladder, yet the possibility of superimposed carcinoma could not be excluded. Hence, after the usual preparation, a low median-line incision was made and a temporary colostomy opening established. The fistula was not visualized nor were there evidences of malignancy. After convalescence the patient was dismissed and advised to return in four to six months; it is hoped that resection may then be made and the colostomy opening closed.

This is another surgical case of diverticulitis and it illustrates the occasional complication of vesical fistula. In the first attack the patient had such complete obstruction that carcinoma was diagnosed. In spite of satisfactory results from medical treatment and watchful care the inflammatory process was reactivated and culminated in perforation into the bladder. It is probable that the colostomy opening will prove to be only a temporary measure and after putting the sigmoid at rest for months,

Fig. 265.—(Case 3.) Diverticulitis of sigmoid; less spasm than on previous examination.

the inflammatory reaction will subside and the fistula close so that further operation may be undertaken at a later date. With such an acute case and the associated bladder trouble, simple medical measures would offer little and colostomy is actually the more conservative treatment.

Case 4.—A man aged sixty-five years had consulted the clinic for several years but not until June, 1926 was there any evidence of bowel trouble

Although he had always been somewhat constipated, abdominal distress was not present until a few weeks prior to this visit. He noted soreness in the left lower part of the abdomen which became fairly severe on one occasion, and was attributed to strain following undue exertion. General examination revealed tenderness over the sigmoid. On account of short stature and obesity examination was not exact. The hemoglobin was 80 per cent and the leukocytes numbered 9,500. A roentgenogram of the colon revealed multiple diverticula with spasm (Fig. 266). Following the usual medical regimen, the

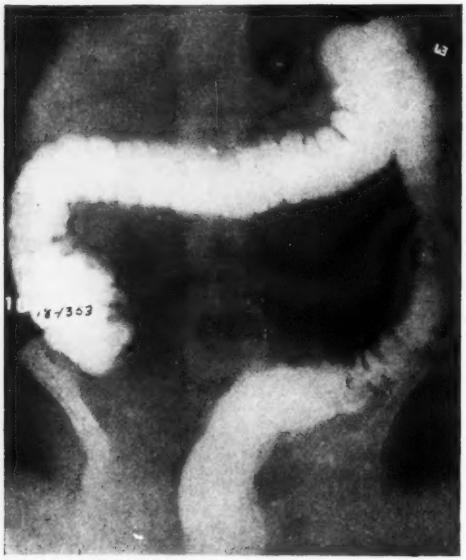

Fig. 266.—(Case 4.) Diverticulitis of sigmoid with moderate degree of spasm.

bowels moved well and all soreness in the side subsided. The patient was reëxamined in April, 1927 and reported that he had not had symptoms referable to the bowel during the preceding ten months. Weight was up to normal, the blood count was normal and the roentgenogram of the colon was unchanged, although there was possibly less spasm than at the first examination. Continued diligence in the care of the bowels was urged.

An examination was made in November, 1928. After the lapse of eighteen months, the patient had not had bowel trouble and but little spasm was shown in the roentgenogram (Fig. 267). The diagnosis of diverticulitis can almost be changed to that of diverticulosis. Some gain in weight (10 pounds) has occurred and he was advised to reduce, at least that amount. The importance of avoiding constipation was reëmphasized.

This case is an excellent example of the satisfactory response to treatment and the thorough coöperation of the patient. The condition is not as acute as in Case 3 nor is there a fistula or a possibility of malignancy. This patient has been very careful

Fig. 267.—(Case 4.) Diverticula and slight spasm of sigmoid.

to see that the constipation is well controlled by simple measures and he thoroughly appreciates the necessity of so doing. It is reasonable to believe that he should get along very nicely. He will be careful to have a reëxamination from time to time.

THE KETOGENIC DIET AND ITS USE

CLIFFORD J. BARBORKA

EPILEPSY

THE greatest recent advance in our knowledge of epilepsy is the demonstration that changes in the physicochemical processes in the body may definitely modify seizures. Epileptic patients have unusual ability to consume and utilize fat; and although there is no definite proof that there is an anomaly in metabolism of fat in epilepsy, when there is incomplete oxidation of fat, ketosis develops and many of the patients are definitely improved. Presumably the beneficial effects of ketosis are not due to changes in acid-base equilibrium alone but also to related changes in the physicochemical reactions of nerve cells with resulting decreased irritability of the nerves. I shall discuss certain matters regarding the ketogenic diet, not to advance a specific therapeutic measure but rather to explain a new and uncertain form of treatment which is in the experimental stage and which should not be allowed to fall into disrepute without a fair trial. Furthermore the ketogenic diet should not escape attention, because, as one of the means of inducing acidosis, it may act physiologically in a manner that will prove to be of therapeutic value in conditions other than epilepsy.

Epilepsy, as the most ancient of nervous disorders, has been recognized for centuries. Perhaps no other malady has brought to the surface so many hypotheses and remedies, all of which have been tried and found wanting. A few of the varied therapeutic measures seemed logical but most of them were empirical and some of them repulsive. For example, in the old days epileptics drank the blood from wounds of dying gladiators because they had heard that once a man who did so was cured. I imagine that many persons will feel that the more modern ketogenic diet is no less troublesome a form of treatment.

Nevertheless, in spite of the difficulties of calculating the ketogenic diet and of educating the patient in the construction of the diet from the dietetic prescription given, and in spite of the sacrifice, faithfulness and determination required on the part of the patient to maintain constant ketosis, it is far better for both physician and patient to undergo these difficulties through which is offered a ray of hope for recovery or for diminution in the frequency and severity of the attacks, than merely to recognize that the condition is epilepsy, to employ a sedative, and to wait.

The apparently hopeless and depressive nature of the affliction has stimulated research in an effort to correlate the mass of good, bad, and indifferent data that have appeared in the literature since the time of Hippocrates. Approximately one out of every 300 persons in the United States is afflicted with epilepsy. The care of these patients is a heavy burden on their families or on the communities in which they reside. The hope has been to discover the cause of the attacks and any possible methods of improving treatment.

Since 1921 special attention has been given to the possibility that there might be a relationship between the acid-base equilibrium of the body and the convulsive seizures, for the attacks are more likely to occur when the reaction of the body fluids tends to be alkaline. Acidosis on the other hand causes, in some patients, reduction in the number or the severity of the seizures.

The complex condition which is known clinically as acidosis can be induced in several ways. Rebreathing, the administration of acid or acid-forming salts, or the induction of ketosis will cause clinical acidosis to develop, and the degree to which the condition has advanced can be ascertained by determining the carbon dioxid combining power of the blood. Ketone bodies (acetone, diacetic acid, and beta-oxybutyric acid) are formed as intermediary products of the incomplete oxidation of fats, when the amount of carbohydrate in the diet is limited. Furthermore, a mild degree of acidosis or, possibly better, ketosis, exists in fasting persons who, after the first day or so, must rely on their

stores of fat and protein. Since the stores of carbohydrate are small, a short fast depletes them and subsequently only the carbohydrate derived from protein is available; this, however, is sufficient to prevent a high degree or dangerous condition of acidosis.

Clinically, it has been known for some time that fasting is beneficial to patients with epilepsy. In most instances patients were free from convulsive seizures during the period of fasting, but the attacks returned sooner or later after the resumption of a normal diet. Obviously it is impracticable to attempt to subject patients to repeated periods of fasting in an effort to maintain ketosis. However, the science of nutrition, and studies on the metabolism of the body, make it possible to plan diets that will be ketogenic. The state of ketosis is produced whenever there is incomplete combustion of fat and there is incomplete combustion of fat whenever the amount of carbohydrate is inordinately reduced. In the ketogenic diet the ketogenic factors, or fatty acid derivatives of foods, overbalance the antiketogenic factors or glucose derivatives of foods. The diet consists of a large amount of fat and a minimal amount of protein and carbohydrate. The fact that large amounts of acetone and diacetic acid are excreted in the urine provides a simple means of insuring that the diet is accomplishing its purpose. More exact data on the extent to which acidosis has advanced can be ascertained by determining the carbon dioxid combining power of the blood.

Clinical and experimental results so far obtained justify further use of the ketogenic diet. For the present, due to the fact that the ketogenic diet and its resulting effects on the tissues of the body are in the experimental stages, the selection of cases for practical purposes should be made on the following criteria: (1) The patient must be in a suitable environment and must have facilities for securing the diet; (2) the attacks of either petit mal or grand mal must be frequent enough to justify some statistical conclusions, over a period of years, regarding the benefit that may or may not be derived; (3) the patient must be willing to spend two or three weeks under direct supervision

so that he may learn individually the manner of maintaining and adjusting the ketogenic diet; and (4) the patient must have the intelligence, willingness, and desire to coöperate to the fullest extent and must understand what can or cannot be hoped for from the regimen. It is unfair to the patient, at the time he starts treatment to offer him this regimen as a cure. No one can foretell, in any individual case, whether or not benefit will result.

The type of case of epilepsy which offers the best opportunity for treatment is that of the child or young adult who is just beginning to have seizures, before the convulsive reaction has become a habit. The type of case in which seizures have been frequent for years, with resultant mental deterioration, is, of course, the least likely to be benefited. Helmholz and Lennox have treated cases of symptomatic epilepsy and have observed enough improvement to believe that this type may be considered suitable for a trial. The patients are, of course, under the constant supervision of a physician.

Two conditions are necessary to the utilization of the ketogenic diet: A simple method of calculating it, and education of the patient in the construction of diets from the calculation. The calculation of a ketogenic diet depends on two principles: the total amount of food given must correspond as closely as possible with the total energy requirements of the patient; the ketosis which involves limitation of the quota of carbohydrates in the diet must be developed and maintained. While using the ketogenic diet at The Mayo Clinic, I devised a method which, although less exact from the standpoint of the theoretic relationship involved, is sufficiently accurate for clinical work and has the advantage of greater simplicity. The resulting diets conform to the theoretic causes of ketosis as developed by Woodyatt and Shaffer. This simple system of calculation cannot be utilized in exact or experimental work when it is desired to study the relationship of the ketogenic to antiketogenic molecules.

Before patients are given the ketogenic diet their total calorie requirements for twenty-four hours must be estimated. For

practical purposes, the energy requirement for each twenty-four hours for the ordinary adult patient is approximately 16 calories for each pound of body weight, and for the ordinary child, 25 calories for each pound of body weight. Thus one can usually obtain a fairly close approximation of the total calorie value of the food needed for adults by multiplying their weight in pounds by 16, and for children by multiplying their weight in pounds by 25. The carbohydrates, protein, and fat are then calculated according to diet 1 (Table 1). This diet is continued for three

TABLE 1

METHOD OF CALCULATION FOR KETOGENIC DIET

Diet.	Carbohydrate, gm.	Protein, gm.	Fat, gm.	Procedure.
1	Estimated calories* × 0.035.	Adult —⅓ weight.† Child —⅔ weight.	Estimated calories × 0.09.	Continue for three to four days.
2	Estimated calories × 0.02.	Adult —⅓ weight. Child— ⅔ weight.	Estimated calories × 0.09.	Continue for one to two days. Intermediate diet prior to production of ketosis, or fast patient for two days and begin Diet 3.
3	Estimated calories × 0.015.	Adult —⅓ weight. Child —⅔ weight.	Estimated calories × 0.10.	Continue for three to five days, ketosis may develop.
4	Estimated calories × 0.010.	Adult —⅓ weight. Child —⅔ weight.	Estimated calories × 0.10.	
5	Estimated calories × 0.008.	Adult —⅓ weight. Child —⅔ weight.	Estimated calories × 0.10.	Continue indefinitely. Diets 4, 5, and 6 to be used in order to develop or intensify ketosis if necessary.
6	Estimated calories × 0.006.	Adult —⅓ weight. Child —⅔ weight.	Estimated calories × 0.10.	Continue indefinitely. Diets 4, 5, and 6 to be used in order to develop or intensify ketosis if necessary.

* Total estimated calories = weight in pounds × 16 for adults; total estimated calories = weight in pounds × 25 for children.
† Weight means weight in pounds.

to four days. Occasionally the sudden change from the normal relatively low-fat diet, on which the average patient now lives, to the low-carbohydrate and high-fat diet may result in nausea or even in vomiting. There will be little difficulty if the change is made gradually. For several days intermediate diets, as diet 2, or sometimes a short fasting period for one or two days, may be interposed before the institution of diets higher in fat (diet 3). If nausea should occur, small amounts of orange juice, which gradually overcome the sensation, may be

prescribed. Diet 3 can be continued for three to five days, as a result of which ketosis usually begins. Diets 4, 5, and 6 are then given in order to intensify the ketosis if this is necessary to control the attacks. The ease of developing and maintaining ketosis and the direct relationship between the degree of improvement and the intensity of ketosis produced differ greatly in different persons and probably vary in the same person from time to time. There is also evidence of the possible relationship of the duration of ketosis and its influence on the epileptiform seizures.

With the development of ketosis and the increased excretion of base, some loss of weight may be expected because of the accompanying dehydration. If, after the diet is found which produces adequate ketosis, the patient's weight does not remain reasonably constant, the calories are raised or lowered depending on whether there has been a gain or loss in weight. The diets thus calculated are on the basis of the total energy required for carrying on normal activities. If, for any reason, the total energy demands are lessened, it is necessary to reduce correspondingly the total calories of the diet and to recalculate the quantity of carbohydrate, protein, and fat on the new basis. Due consideration must be given to the constituents of the normal, adequate diet; that is, protein sufficient to replace the nitrogenous waste and to build new tissues, minerals, and vitamins must be given.

Patients must be carefully and systematically trained for this treatment, as it has been found necessary to train them for the proper management of diabetes. While the diet is being adjusted the patient is learning how to use a set of scales, how to use food tables, and how to translate the diet prescription which calls for grams of carbohydrate, protein, and fat into meals and into terms of vegetables, fruits, eggs, and other foodstuffs. This at first seems difficult, and for this reason patients are asked to stay four weeks for the instruction which is the most important part of the treatment. Patients who have only limited educational advantages are trained sufficiently to take care of themselves. Diet order forms (Tables 2, 3, and 4) are prepared

TABLE 2

KETOGENIC DIET: THE MAYO CLINIC

Adult patient, weight 156 pounds, diet 2

Carbohydrate 50.2 gm., Protein 52 gm., Fat 224 gm., Calories 2,433

Food.	Breakfast, gm.	Dinner, gm.	Supper, gm.	Total, gm.	Carbohydrate, gm.	Protein, gm.	Fat, gm.	Woodyatt F. A.: G. Ratio 2.2 : 1
								Breakfast
Vegetables:								Orange, 90 gm.
Canned tomato		100		100	3	1		White bread, toasted, 19 gm.
Carrots			50	50	5	0.5		Butter, 20 gm.
Fresh cabbage		60		60	3	1		Forty per cent cream, 50 gm.
								Bacon, crisp, 20 gm.
Fruits:								Egg, 1.
Orange	90		70	160	16			Dinner
Pear		60		60	6			Roast lamb, 60 gm.
								Canned tomato, 100 gm.
Bran soya muffins		1*	1*	2*	1.2	8	14	Bran soya muffin, 1.
Cream 40 per cent	50	75	75	200	6	4	80	Butter, 32 gm.
Bacon, crisp	20		10	30		6	15	Forty per cent cream, 75 gm.
Eggs	1*		2*	3*		18	18	Pear, 60 gm.
								Supper
Meat:								Eggs, 2.
Roast lamb		60		60		12	8	Bacon, crisp, 10 gm.
Butter	20	32	32	84			70	Carrots, 50 gm.
Mayonnaise		24		24			20	Fresh cabbage, 60 gm.
Bread, white	19			19	10	1.5	0.5	Mayonnaise, 24 gm.
								Bran soya muffin, 1.
								Butter, 32 gm.
								Forty per cent cream, 75 gm.
								Orange, 70 gm.

* Unit, not gm.

TABLE 3

KETOGENIC DIET: THE MAYO CLINIC

Adult patient, weight 156 pounds, diet 4

Carbohydrate 25.3 gm., Protein 51.5 gm., Fat 250 gm., Calories 2,558

Food.	Breakfast, gm.	Dinner, gm.	Supper, gm.	Total, gm.	Carbohydrate, gm.	Protein, gm.	Fat, gm.	Woodyatt F. A.: G. Ratio 3.1 : 1
								Breakfast
Vegetables:								Orange, 30 gm.
Swiss chard		60		60	3	2		Bran soya muffin, 1.
Tomato		50		50	1.5	0.5		Butter, 19 gm.
Celery			100	100	3	1		Forty per cent cream, 100 gm.
								Bacon, crisp, 10 gm.
Fruits:								Dinner
Orange	30			30	3			Roast chicken, 62 gm.
Pineapple			40	40	4			Swiss chard, 60 gm.
								Tomato, 50 gm.
Bran soya muffins	1	1	1	3	1.8	12	21	Mayonnaise, 24 gm.
Cream, 40 per cent	100	100	100	300	9	6	120	Bran soya muffin, 1.
Bacon, crisp	10			10		2	5	Butter, 30 gm.
Eggs			1	1		6	6	Forty per cent cream, 100 gm.
								Supper
Meat:								Dried beef, 33 gm.
Chicken		62		62		12	10	Egg, 1.
Dried beef			33	33		10	2	Celery, 100 gm.
Mayonnaise		24		24			20	Bran soya muffin, 1.
Butter	19	30	30	79			66	Butter, 30 gm.
								Forty per cent cream, 100 gm.

TABLE 4

KETOGENIC DIET: THE MAYO CLINIC

Adult patient, weight 156 pounds, diet 6

Carbohydrate 15.2 gm., Protein 52.5 gm., Fat 250.5 gm., Calories 2,518

Food.	Breakfast, gm.	Dinner, gm.	Supper, gm.	Total, gm.	Carbohydrate, gm.	Protein, gm.	Fat, gm.
Vegetables:							
Sauerkraut		50		50	1.5	1	
Tomato and lettuce			50	50	1.5	0.5	
Fruits:							
Strawberries	40			40	2		
D'Zerta*				1		2	
Bran soya muffins	1	0.5	0.5	2	1.2	8	14
Cream, 40 per cent	100	100	100	300	9	6	120
Bacon, crisp	25			25		5	12.5
Eggs	2		1	3		18	18
Meat:							
Pork chop		70		70		12	14
Mayonnaise			24	24			20
Butter	12	25	25	62			52

Woodyatt F. A.: G. Ratio 3.6 : 1

Breakfast
Strawberries, 40 gm.
Bran soya muffin, 1.
Butter, 12 gm.
Forty per cent cream, 100 gm.
Bacon, crisp, 25 gm.
Eggs 2

Dinner
Pork chop, 70 gm.
Sauerkraut, 50 gm.
Bran soya muffin, 0.5.
Butter, 25 gm.
Forty per cent cream, 100 gm.
D'Zerta,* 1.

Supper
Egg, 1.
Tomato and head lettuce, 50 gm.
Mayonnaise, 24 gm.
Bran soya muffin, 0.5.
Butter, 25 gm.
Forty per cent cream, 100 gm.

* D'Zerta is carbohydrate-free gelatin.

in duplicate by the dietitian whenever the prescription is changed. These forms show the dietary prescription for the day, the kind of food used, and the amount in grams. They offer a convenient way of planning meals. The names of the foods are written in the food column, then the tables are consulted for advice as to the composition of the food chosen, and the amounts of each foodstuff are given so that the final total of protein, carbohydrate, and fat agrees with the prescription. Food is not allowed except that which the diet order permits. This rule covers not only the usual foods but also chewing gum, chewing tobacco, and alcohol. Patients are taught to examine the urine daily to determine whether acetone bodies are being excreted, thus assuring themselves that they are in a state of ketosis. The degree of the intensity of color in the tests for ketone bodies gives a rough approximation of the intensity of ketosis. The patients keep records of the attacks of petit mal and grand mal.

If the convulsive seizures persist for a month or two in

spite of the ketosis, a period of absolute starvation of seven to ten days can be tried. During this fast, only the juice of one orange is given daily. Following starvation the ketogenic diet is gradually resumed. At the end of six months it is generally possible to determine whether or not benefit has accrued. However, in a few cases that have been controlled, benefit did not occur until strict ketosis had been maintained for eight months to a year.

It is not known as yet whether or not the patient must always maintain a strict ketogenic diet. There is some evidence that a milder degree of ketosis may be sufficient. Whether or not there can be a resumption of a diet in which there are more nearly normal proportions of carbohydrate and fat will depend on the individual case. If the attacks recur when the intensity of ketosis is reduced, a diet should be maintained which produces a degree of ketosis adequate to control the attacks.

Certain difficulties are encountered in the use of the ketogenic diet which are worthy of note:

1. The education of the patient, which already has been presented.

2. Infringement on the rules of diet as the result of failure to convince the patient of the importance of small deviations or lack of coöperation.

3. The calculation of the diet so as to maintain ketosis in persons of varied occupations who have different energy requirements for work and exercise.

4. The sensation of hunger due to lack of bulk in the diet; this can be obviated by the use of bran, agar jelly, and gelatin as fillers.

5. The difficulty of incorporating large amounts of fat in the diet, since the chief supply must come from cream, butter, bacon, olive oil (plain or in mayonnaise), and cod-liver oil.

6. The presence of constipation. Since constipation is commonly associated with epilepsy and seems to predispose to an attack, it is desirable to insure good elimination. The ketogenic diet is in itself somewhat laxative so that cathartics should not be necessary. If they are necessary, however, the selection

should be limited to plain granular agar, various mineral oils, salts (Carlsbad or magnesium sulphate), and the bitter fluid extract of cascara. Any of these may be used to aid in establishing regularity of defecation and should be withdrawn as soon as possible. However, magnesium sulphate by mouth, in a 50 per cent solution, is especially valuable as it serves the triple purpose of cleaning out the bowels, increasing acidosis, and reducing cerebral edema and intracranial pressure.

7. The nausea or vomiting occasionally resulting at the beginning of the ketogenic diet. It results from the sudden change from the normal or high-carbohydrate diet, on which the average epileptic patient lives today, to the low-carbohydrate and high-fat diet. This, as pointed out, may be avoided by gradual change in the proportions of carbohydrate and fat.

In addition to the diet the treatment should include everything to soothe and quiet the patient. There should be regulated periods of exercise alternating with periods of rest and repose. After the development of the disease, assistance may be rendered by a suitably trained nurse or companion, and it may be necessary to remove the patient from home environment.

Effort should be made to train epileptics, especially the younger patients, along suitable physical, educational, and psychologic lines to meet the fundamental demands of life. The epileptic patient should be educated to adapt himself to the stresses and difficulties of life, whether these are met with at home, in school, at work, or in business, or whether they are ethical, social, or moral.

Epileptic patients are likely to suffer from lowered vitality and sluggish circulation for which warm baths and massage are beneficial. In all cases, a certain amount of open-air recreation is most important. All occupations fraught with danger, such as driving automobiles or handling machinery, obviously are most unsuitable. For the robust epileptic person such occupations as poultry farming and market gardening are suitable.

In reiteration it may be said that the ketogenic diet has been of some value in a certain percentage of cases and is worthy of careful investigation and careful study. Judgment as to the

ultimate value of the ketogenic diet in the treatment of epilepsy can be given only after time for its further employment has elapsed.

MIGRAINE

The relationship between epilepsy and migraine has been noticed for years and must be considered. Some believe that both of these conditions are due to the same etiologic factor expressed in a different manner, that attacks of migraine are a sensory seizure whereas epilepsy is a motor seizure. However, there are very few cases in which epilepsy coincides with migraine. Cases occur in which epilepsy succeeds or alternates with migraine but they are exceptional. Migraine is a rather common syndrome and it is not surprising that a certain number of epileptic patients should also have migraine. Because of the fact that so many authors have noticed the close relationship between the two constitutional anomalies, early in the experience with the ketogenic diet at the clinic it was tried in cases of migraine. Since publication of the 1928 Mayo Clinic number of the Medical Clinics of North America, in which attention was called to the use of the ketogenic regimen in migraine, Lennox and Cobb, in their monograph on epilepsy, have stated that it will be of interest to know if the induction of acidosis is of benefit in this condition. Schnabel has recently discussed his experience with a ketogenic dietary in migraine.

Migraine and epilepsy have equivalent etiologic and pathologic factors in that no one has as yet demonstrated a consistent pathologic lesion or formulated a theory of a constant mechanism of production of the symptoms of either condition. Some of the recent therapeutic suggestions and etiologic theories will be mentioned in the following sentences. The first group has to do with the changes in acid-base equilibrium. Cases of migraine are benefited by fasting with its accompanying starvation acidosis. R. and S. Weissmann, Netherlands, found apparent changes in the acid-base balance in migraine; the hydrogen-ion concentration and alkaline reserve are normal in the periods of freedom from attacks but a tendency to alkalosis develops forty-eight hours prior to an attack. The recent method of studying

acid-base equilibrium by hyperpnea, or over-ventilation of the lungs, which induces alkalosis, was utilized by Muck who produced hemicranial attacks in patients subject to migraine. Bigland has called attention to the use of large doses of calcium lactate in an effort to lessen the irritability of the nerves. The second group is concerned with allergy. Vaughan, Rowe, Miller, Rawlston, and many others have discussed migraine from the standpoint of an allergic manifestation of an inherited impaired metabolism that is intolerant of nitrogenous foods, a protein-poison theory. They advocate various forms of treatment, from the use of peptone to the restriction of certain proteins. Many patients themselves restrict carbohydrate, protein, or fat in their diet after finding that over-indulgence in one of the three elements of foodstuffs has been followed by a sick headache. Of these three, over-indulgence in carbohydrate is the most likely to precipitate an attack. The third group takes account of dysfunction of the liver and duodenum. Diamond, Hetinyi, McClure, Huntsinger, and others have called attention to the evidence of disturbed hepatic function as estimated by the van den Bergh reaction and bilirubin retention. Many patients were improved by the intraduodenal administration of magnesium sulphate to stimulate the flow of bile.

With these facts in mind it can be seen more readily that the use of the ketogenic diet in migraine is not without logic, as it potentially could cover, in a therapeutic manner, all three of the foregoing suggestions at the same time. If alkalosis induces migraine, the ketogenic diet which produces acidosis, with an accompanying decrease in irritability of nerves, might be expected to inhibit the attacks. From the standpoint of an allergic manifestation it is very possible that there is a chance withdrawal of the specific protein, and there is also marked restriction of carbohydrate. Boyden has shown that a diet high in fats promotes biliary drainage, and it has been demonstrated also that duodenal motility occurs after ingestion of fat. Therefore we would expect benefit in the cases due to dysfunction of the liver or duodenum.

As in epilepsy, it is well to make a careful selection of cases

and to vary the intensity of ketosis with the severity and frequency of the attacks. At the present time at the clinic cases are being divided into three groups, and only those cases that are definitely instances of migraine without associated lesions are considered. In the first group attacks are mild and not too frequent, perhaps one a month or one in two months, and in the case of female patients the attacks are usually associated with the menstrual period. In these cases a diet is first attempted that is on the borderline of ketosis and it is noted whether the restriction is sufficient to be of benefit. Such a diet, calculated for an adult weighing 156 pounds would be, as illustrated in Table 2, carbohydrate, 50 gm., protein, 52 gm., and fat 225 gm. If the attacks are not improved and ketosis does develop after a few months on the diet, the ketosis is intensified by reducing the carbohydrate and increasing the fat, as in diets 3, 4, or 5 (Table 1).

The second group is composed of patients whose attacks are severe, occurring at least once or twice a month, and in women the attacks are without any definite relation to the menstrual period. In this group the diet should be gradually altered to the point where it will insure ketosis, which ordinarily will require at least diet 4. An illustration of diet 4, for a patient weighing 156 pounds, is found in Table 3.

The last group is made up of patients who have very severe and frequent attacks. These patients usually have resorted to all types of medical treatment, and sometimes to surgical procedures without any benefit. They are desperate, and are willing to attempt any procedure, regardless of the effort involved. In such cases it is necessary to intensify the ketosis, and an example of the final diet employed in the treatment of these patients is demonstrated in Table 4.

As yet, the number of cases that has been treated at the clinic is not large enough to warrant evaluation of the therapeutic results obtained. Thus far the benefits derived have been sufficiently encouraging to justify the further use of the ketogenic diet in the treatment of migraine.

In following the cases of epilepsy and migraine among adult

women who have been treated by the ketogenic diet, it has been noticed that in a large number there is cessation of the menses. In some cases the menses have ceased following the first development of ketosis, whereas in others they will not cease until several months have passed. It is impossible to anticipate in which patients cessation of the menses will follow ketosis, and in a few cases there is no influence whatever on the amount or regularity of the menstrual flow. This observation calls attention to the possible influence of high-fat feeding on the hormones that may be responsible for the menstrual cycle. It also brings up the question as to whether the periods will return after resumption of a more normal diet. A few patients whose menses have ceased have been allowed to return to a normal diet, and within a few months' time there was a return of normal menstrual periods. Whether this will occur in all patients is not known. In the case of epilepsy, one is not so much concerned regarding the return of the menses; many of these patients do not desire children because of the possible tendency to hereditary transmission of the disease. In the case of patients with migraine the outlook is entirely different. Therefore, it is well to caution patients, before treatment, regarding this possibility. In three cases of migraine with associated menorrhagia, and without any pathologic condition in the pelvis, there was complete cessation of the menstrual flow in addition to control of the migraine while the patients remained on the diet. This influence, combined with the effects on the normal menstrual period, has caused the ketogenic diet to be used in selected cases of young women who are suffering from menorrhagia without abnormalities in the pelvis. Data on this aspect of the work are being gathered in preparation of a further report.

SUMMARY

Physicians should think of the ketogenic diet as a form of treatment to be applied quantitatively to selected cases as an accurately controlled experiment rather than as a proved specific remedy to be used in all cases of epilepsy and migraine. The term "ketogenic diet" which may be confusing to the average

physician who is not working in the field of metabolism, merely denotes a diet having high-fat and low-carbohydrate constituents in definite but varied proportions which results in the excretion of ketone bodies. This form of treatment influences the acid-base balance and produces certain physicochemical changes in the tissues of the body which deserve a great deal of further investigation and study.

CALCINOSIS AND SCLERODERMA IN A CHILD TREATED BY KETOGENIC DIET

R. L. J. KENNEDY

DEPOSITS of calcium have been observed virtually in all tissues of the body. Deposits in the skin and subcutaneous tissues have been reported either as a primary or a secondary condition, or as an accompaniment to other conditions, particularly scleroderma. Although calcinosis, as this phenomenon has been termed, is not common, reports have been made from many parts of the world which give details of cases, and which offer various hypotheses as to the cause. To supplement the clinical and anatomic observations, a considerable amount of experimental work has been done, the results of which have been used to support certain of the hypotheses formulated in explanation of the etiology and pathogenesis.

Durham recently reported a case of scleroderma and calcinosis with a review of the literature on the historic aspects and a consideration of the various theories on etiology and pathogenesis. My interest in the subject was aroused by the examination of a child aged six years in whom there was rather marked scleroderma and calcinosis, and because of the adoption of a rather unusual form of treatment.

The treatment of calcinosis heretofore has been based on rather poorly substantiated hypotheses of its pathogenesis. Thus, on the hypothesis that it is due to parathyroid dysfunction, certain clinicians have given parathyroid preparations. However, since none of these hypotheses has withstood close examination it may be said that a rational treatment has not been discovered.

Frölich reported a case of progressive myositis ossificans, treated by means of a diet high in fat. He offered two observations: First, it has been known for a long time that fractured

bones of diabetic patients heal slowly and with difficulty, a fact that leads to the assumption that acidotic metabolism hinders calcification of newly formed bone; second, certain problems of research show that metabolism of rachitic infants is acidotic and that this acidosis is of great importance in preventing significance in the prevention of calcium salts from being deposited in the zone of ossification.

Frölich believed, therefore, that in spite of the fact that one is unable to prevent myositis, it might be possible, by acidotic metabolism, to prevent the deposition of calcium salts in the intramuscular tumors formed by the hyperplasia of the intermuscular and intramuscular connective tissue. Frölich's patient was a child aged two years and nine months. The onset of the condition had occurred at the age of one year and at the time treatment was begun progressive myositis ossificans was well developed. After eighteen months of dietary treatment some of the masses had disappeared, new masses had not appeared, and motion had improved greatly.

Nelson recently reported the results of determinations of calcium and phosphorus intake and output in three epileptic children receiving the ketogenic diet. In each instance the output of calcium and phosphorus exceeded the intake. The observations were made over a short period.

REPORT OF A CASE OBSERVED IN THE MAYO CLINIC

A girl aged six years was brought to the clinic in September, 1928 because of masses in the skin of the elbows, axillæ, and back, and because of difficulty in walking. The mother and two other children were living and well; the father had died two years before from "manic-depressive insanity and cardiac exhaustion." The mother had had two miscarriages before the birth of the patient who was a normal baby. The patient's appetite had been poor and there had been some difficulty in feeding her. She had had frequent attacks of vomiting until the age of five years. In September, 1926, instability and difficulty in walking had been noted, and this had continued for a few weeks, during which time various types of shoes were worn. On the advice of a physician she had been placed in bed and did not walk for a year. Several physicians had felt that the chief factor was hysteria. While she was in the hospital scarlet fever had developed and her strength had been slow in returning. In April, 1927, tonsils and adenoids had been removed. Casts with wedging had been applied in order to overcome the ham-string contractures which had occurred during her stay in the hospital. Braces

had been applied later, enabling her to walk. At the time of examination they were worn half of the day. If the braces were left off for a period of two weeks, there seemed to be a tendency for the return of contracture at the knees. In September, 1927, small, hard masses had begun to appear under the skin, first in the anticubital spaces, later in the popliteal spaces, in the region of the hips, and over the lower portion of the spine. These gradually had become more prominent and numerous but did not cause symptoms. During rainy or damp weather temporary contracture and cramping of the hands occurred.

Examination showed the child to be in a fair state of nutrition and weighing 42 pounds. She was alert and coöperative. The teeth were discolored and crowded; the palate was high and arched. In the axillæ, and anticubital and popliteal spaces, over the lower part of the spine, and surrounding the region of the pelvis were firm, bony hard deposits apparently in the subcutaneous tissue. The skin in these regions was smooth, rather

Fig. 268.—Calcification of the skin and subcutaneous tissue.

shiny and firm. There was marked limitation of motion in most of the joints, especially in the hips, knees, elbows, and shoulders; the gait was peculiar and stiff-legged. The urinalysis was negative. The hemoglobin was 63 per cent, erythrocytes numbered 3,830,000, leukocytes 5,900, lymphocytes were 33 per cent, large mononuclear leukocytes 2 per cent, transitionals 1.5 per cent, neutrophils 62 per cent, eosinophils 1 per cent, and basophils 0.5 per cent. The Wassermann test on the blood, and the von Pirquet test were negative. The serum calcium was 10.8 mg. for each 100 c.c. (normal, 10 mg. for each 100 c.c.); the serum phosphorus was 4.2 mg. for each 100 c.c. (normal, 5 mg. for each 100 c.c.). Roentgenograms of the chest and skull were negative. Roentgenograms of the trunk and extremities showed calcification of the skin and subcutaneous tissue around the lower part of the pelvis and in the arms, forearms, axillæ, and around the knees (Fig. 268). The roentgenogram suggested the diagnosis of scleroderma. There was no roentgenologic evidence of disease of the joints or bones.

The child was placed on the ketogenic diet, as described by Helmholz, and at the end of the first week was receiving carbohydrate 14 gm., protein 20 gm., and fat 140 gm., and was permitted to return home. Her weight at this time was 39 pounds, a loss of 3 pounds since the commencement of the diet. This loss of weight occurs in nearly all children during the first two or three weeks on the diet.

One and a half months later the mother reported that the child was walking without braces. Diminution in the size of the masses in the skin was not apparent although they seemed somewhat softer. There was slight pain in the region of one of the masses in the right arm, and in the right lumbar region. The weight had remained at 39 pounds. Two and a half months later the child had gained 1.5 pounds after the diet had been changed to 14 gm. carbohydrate, 25 gm. protein, and 155 gm. fat. She was still walking without braces. The advent of cold weather had caused the return of some pain in the left arm. Three and a half months later the weight was 43.5 pounds, a gain of 1.5 pounds since commencement of the diet. The stiffness which had formerly appeared after sitting had disappeared and the child was walking better. Her general condition was better and her color was good.

During all this time the urine had tested positively for acetone and diacetic acid. The reports of improvement were from observations by the parents and the extent of the improvement cannot be estimated accurately.

COMMENT

Of twelve cases of combined scleroderma and calcinosis reviewed by Durham, only two were observed in children, although four of the twelve were said to have begun in childhood. Hence, this case may be considered unusual.

The use of the ketogenic diet is new, although almost entirely empirical. Neither Frölich's nor Nelson's observations are sufficiently conclusive to establish the diet on a firm basis as a therapeutic agent. It may be emphasized that the etiology and pathogenesis of calcinosis in scleroderma and other conditions are unknown. If the ketogenic diet proves efficacious in treatment its use should be continued, although its value may at present be doubtful, and although the explanation of favorable results may be made only with reservations.

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PERINEPHRITIC ABSCESS

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PERINEPHRITIC abscess usually results from one of two causes: It may be secondary to pyonephrosis, lithiasis, tuberculosis or traumatic rupture, or it may follow metastasis from distant foci of infection to the renal cortex. If the former, attention is usually focused on the kidney, and with the help of roentgenograms and urinary data the condition is not likely to be overlooked. In the metastatic type, however, the onset is usually insidious and in the early stages localizing signs may not be present, so that in the presence of sepsis the condition must always be kept in mind in order that the diagnosis may be made promptly.

REPORT OF CASES

Case 1.—A man aged twenty-nine years had always been well until June, 1924 when a carbuncle formed on the left buttock. This was incised and healing was rapid. During the latter part of August a second carbuncle appeared on the left buttock. Two incisions were made. A rather marked systemic reaction occurred, and healing was slow. In the early part of September he noted lack of ambition, chilly sensations, loss of appetite, was easily tired and had daily fever varying between 99.5° and 100.5° F. He lost weight rapidly and his friends told him he was looking bad. He feared that he might have tuberculosis. He consulted a physician who had a roentgenogram made of the chest. This was reported as negative. His condition then became worse rapidly. September 25, he had a severe chill followed by a temperature of 104° F. He was then admitted to a hospital in his home town. During the next four weeks the daily temperature was septic in type, varying between 99° F. in the morning and 104° F. in the afternoon. The steady, dull aching pain in the back localized in the right costovertebral angle. There was not, however, any tenderness on deep palpation or hammer percussion. The leukocyte count varied between 9,000 and 22,500. The urine was normal except for a trace of albumin. General examination, including laboratory studies and three cultures of the blood, failed to reveal the cause of the illness.

When the patient was examined October 26 he had lost 40 pounds in weight. The temperature was 101.2° F., and the pulse rate was 140. He

complained of severe pain over the area of the right kidney but there was no tenderness on palpation and a mass could not be felt. The hemoglobin was 60 per cent (Dare), the erythrocytes numbered 3,420,000 and the leukocytes 23,200, of which 90 per cent were polymorphonuclear leukocytes. The urine was normal and aside from the marked appearance of sepsis the general examination was negative. A diagnosis of perinephritic abscess was made and operation advised.

October 27, exploration revealed a large perinephritic abscess, containing about 500 c.c. of thick pus; it had originated from a cortical abscess at the upper pole of the right kidney. Before operation a small amount of bloody sputum had been expectorated; this persisted for several days following operation. Clinical examination and roentgenograms seemed to indicate extension of the abscess through the diaphragm to the base of the right lung. Following drainage of the abscess the patient had a normal convalescence and was dismissed from the hospital on the fourteenth day.

Case 2.—A man aged thirty-one years came to the clinic October 26, 1928. He stated that for two weeks he had had a dull aching pain in the region of the right kidney which was becoming gradually worse. For a week he had had fever, chills and night sweats. His appetite was poor, he had lost weight and he was unable to work. On direct questioning he stated that two weeks before the onset of the present symptoms he had had a boil on the left wrist. This had caused some swelling of the arm with soreness in the axilla. The boil was incised and at the time of the initial examination had completely healed. Thinking it was not significant he had failed to mention it when the history was taken.

The general examination was negative except for moderate tenderness over the right kidney both anteriorly and posteriorly. The kidney was not palpable and a mass could not be felt. The urinalysis was negative and the leukocyte count was 22,000. The temperature was 102° F. A diagnosis of perinephritic abscess was made and operation advised.

Exploration of the right kidney disclosed slight perinephritis and on opening the capsule an abscess at the lower pole containing 15 c.c. of thick yellow pus was found. Drainage of the abscess resulted in recovery. The patient left the hospital on the fifteenth day.

Case 3.—A man aged forty-nine years came to the clinic November 29, 1922. Nine weeks previous to admission a large abscess on the left thigh had been incised and it had drained for two weeks. Three weeks after the abscess appeared, dull, aching, constant pain radiating to the right leg developed in the right costovertebral angle. He had had fever, chills, and poor appetite, and had lost 20 pounds in weight.

Examination revealed a large tender mass bulging posteriorly and extending to the crest of the ilium anteriorly. The urine contained a few pus cells and a few hyaline and granular casts. The leukocyte count was 25,000. A diagnosis of perinephritic abscess was made and it was drained immediately. The patient convalesced normally.

COMMENT

A characteristic feature of the metastatic type of perinephritic abscess is its relation to superficial infections, such as boils, carbuncles, abscess, and paronychia. In practically all instances antecedent infections will be found or a history of them obtained. Frequently such a history is only brought out on direct questioning, as the infection may have been so mild that the patient considered it of no consequence; or it may have occurred months previously and be entirely forgotten. Organisms from superficial infections frequently enter the blood stream and find their way into the kidneys. As a rule they are excreted without doing any harm, but if the patient's general resistance is lowered or the number of organisms is large and their virulence high, lesions are produced which may go on to abscess formation.

Cortical abscess is the most common cause of perinephritic abscess. If the diagnosis is made early the lesion may be confined almost entirely within the renal capsule (Case 2). It is not until the abscess has enlarged sufficiently to reach the periphery of the kidney that it breaks through the renal capsule and forms a perinephritic abscess. The fibrofatty capsule of the kidney is lax and cellular and not extremely vascular, and offers little resistance to the spreading infection. Direct extension of infections from the lower part of the urinary tract and genitalia by way of the lymphatics without renal involvement accounts for a small number of perinephritic abscesses.

The clinical course of perinephritic abscess is best divided into two stages, that of symptoms only, and that of symptoms and localizing signs. The onset may be sudden with a severe chill, high temperature and generalized aching. In the absence of localizing symptoms, the condition may be easily mistaken for influenza. However, the usual onset is insidious; the patient is easily fatigued, he feels out of sorts, perspires easily, often has sensations of chilliness, and slight fever, reaching as high as 100° F., especially in the afternoon. During this stage, which lasts one to four weeks, the appetite is lost, with consequent loss of weight, and a slight degree of secondary anemia is evident. The leukocyte count may be normal or slightly elevated, and

there may be urinary frequency or nocturia. Nausea and even vomiting are not uncommon. During this stage localizing symptoms usually are not present and because of the continuous afternoon fever and the rather rapid decline in the patient's general health, tuberculosis or typhoid fever is often suspected.

After a variable length of time during which the patient may have become bedridden, elevation of temperature continuing or increasing, localizing signs in the renal area or thorax develop. The patient usually complains of a steady, dull aching type of pain in the costovertebral angle on the affected side. This pain is mild at first and may be relieved by aspirin and heat but gradually becomes so severe that codein or even morphin is required. Tenderness over the renal area anteriorly and over the lumbar muscles posteriorly on pressure is the rule. However, at times tenderness cannot be elicited. If the abscess happens to be large or is situated at the upper pole, elevation of the diaphragm and compression of the lung may result in signs indicating pleural effusion or pneumonia. Actual pulmonary complications, such as bronchopneumonia, pleural effusion and pulmonary abscess, are not infrequent. If a mass becomes palpable, the diagnosis is simpler; however, this sign is present only in about two-thirds of the cases. During this stage of the disease the leukocyte count is uniformly high; the temperature is remittent, reaching as high as 105° F. in the evening. Daily chills are not uncommon. The urine is usually normal except for varying amounts of albumin; occasionally red blood cells and pus cells will be noted on microscopic examination.

The diagnosis can rarely be made before localizing signs have developed but fortunately these signs develop before serious complications result. Given a patient with the physical signs of sepsis, a localized pain in the area of the kidney, and a history of antecedent infection, the diagnosis should not be difficult. Carty and, more recently, Lipsett and Beer have called attention to the roentgenogram as an aid in diagnosis. This may show a curvature of the spine with the convexity away from the abscess. Obliteration of the psoas shadow as seen in the roentgenogram on the affected side is also of frequent diagnostic aid.

Early diagnosis is extremely important so that serious complications such as generalized sepsis, abscess of the lung and destruction of the kidney may be avoided.

I have recently reviewed forty-four cases of the metastatic type of perinephritic abscesses seen at The Mayo Clinic. The ages of the patients in this group varied between fourteen and sixty-three; 70 per cent were in the second, third, and fourth decades. The disease occurred most frequently between the ages of twenty and thirty. Thirty-six of the patients were males and eight females, a ratio of 4.5 : 1. The time between the onset of symptoms and surgical treatment varied between one and forty weeks, the average being five and six-tenths weeks. There was a significant loss of weight in all cases. The urine was normal except for a trace of albumin and an occasional pus cell; in one specimen sugar was found. The hemoglobin varied between 30 and 88 per cent, the average being 53 per cent. The leukocyte count varied between 12,800 and 34,400. The abscess was found on the right side in thirty-one cases and on the left in twelve, a ratio of 2.5 : 1. In one case there were bilateral abscesses. The temperature varied between 99° and 105° F. The temperature was normal in an average time of five days following drainage of the abscess. Pain over the site of the infection was present in all cases. In three cases there was no tenderness over the area of the abscess on palpation. In thirty cases (69 per cent) tumor was palpable. In seven cases roentgenograms and physical signs indicated elevation of the diaphragm on the affected side.

The treatment of perinephritic abscess is simple drainage and if this is done early the outcome should be uniformly good.

WATER INTOXICATION IN CASES OF DIABETES INSIPIDUS

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IT has been shown by Rowntree, Weir, and their associates[7, 9] that the administration of water to mammals in hourly doses of 50 c.c. for each kilogram of body weight will produce ataxia, vomiting, and convulsions. Further studies on this peculiar type of intoxication have been carried out by Greene and Rowntree[5]; they showed that these phenomena are probably due to two factors: actual dilution of the blood, and increased water in the tissues, particularly the central nervous system. Water intoxication in the human being was probably produced by the water torture of the middle ages, but until recently a clinical counterpart of the condition has not been observed or described. Miller and Williams, however, have shown that unpleasant symptoms may follow excessive fluid intake, and Rowntree's original work was begun as a result of the observation of the cerebral symptoms of a patient with diabetes insipidus who took as an experiment a large quantity of fluid while the output of urine was kept at a minimum by the use of pituitrin.

There seems to be no reason why, in cases of diabetes insipidus, dilution of the blood and waterlogging of the viscera should not develop but, nevertheless, most patients with this disease do remarkably well, suffering only from the inconvenience of polydipsia and polyuria. The explanation probably lies in the fact that the concentration of sodium chlorid is not reduced (as occurs in the experimental animal), the urine being practically pure water with a low content of salts and other solids. The phenomenon of water intoxication may occur in man under certain conditions. I shall discuss here three cases and discuss the basic conditions which seem to be associated.

Snell and Rowntree, in 1927, reported a case of diabetes insipidus secondary to epidemic encephalitis, in which there was both clinical and laboratory evidence of water intoxication. This case is briefly described here principally because of the fairly definite evidence of chemical changes in the blood which confirmed the diagnosis.

Case 1.—A man aged twenty-seven years had had the initial symptoms of epidemic encephalitis in 1923. At that time he had been advised to increase intake of fluid and a sort of compulsion thirst developed rapidly, which prompted him to take as much as 24 liters of water a day. After three years of gradual deterioration and the appearance of parkinsonian rigidity and tremor, the patient had attempted a "water cure" on his own initiative. He drank ice water as fast as he could until he vomited and fell to the ground in a convulsion, a bucket in his hands. He had repeated this heroic measure no less than seven times, with the same result each time.

On examination, the characteristic postencephalitic Parkinson's syndrome and secondary diabetes insipidus were noted, and the patient was hospitalized for study and treatment. Two striking features were apparent: (1) A great variation of intake of fluid and output of urine, relatively unaffected by pituitrin, with corresponding changes in body weight, and (2) extreme coldness of the surface of the body, with cold cyanotic extremities. After the patient had received pituitrin on two successive days in the hospital, uncontrollable thirst developed, and in spite of repeated warnings the intake exceeded the output by more than 12 liters during a period of thirty-six hours. At the end of this time he was confused, restless, and said he was about to have a convulsion; this, however, was avoided by confining him under strict surveillance by the use of phenobarbital. Laboratory studies at this time showed definite evidence of dilution of the blood, the serum protein being reduced 13 per cent, the blood sodium 27 per cent, and the serum chlorids 20 per cent. Since these data correspond exactly with those of experimental animals during water intoxication, it was believed that the patient was undoubtedly suffering from the same type of disturbance.

The patient has kept us informed of his progress for nearly two years; he has never had another convulsion, but has kept his compulsion thirst under control only with great difficulty. The parkinsonian syndrome has become progressively worse, but the fluid exchange is much smaller than at the time of his examination.

In Cases 2 and 3 the convulsions which were presumably due to water intoxication occurred while the patient was under observation. Although laboratory evidence of dilution of blood was not obtained in either case, the circumstances under which the condition developed seem to make the diagnosis indisputable.

Case 2.—A man aged twenty-three years came to the clinic in October, 1928 complaining of weakness, nervousness, and occasional convulsions. His illness had begun four years previously with some obscure disorder, which confined him to bed for several weeks. Appendectomy was performed at that time without change in his general condition. As the initial illness was subsiding, he was advised by his physician to take more fluids. He had carried out this advice with a will, and on occasions had taken 24 liters of ice water in twenty-four hours. This excessive intake of fluid had been kept up with minor modifications for a period of four years. On several occasions, generalized edema had developed and after the edema had been present for several days convulsions of an epileptiform nature occurred. He had found that the convulsions could be avoided if he induced vomiting and he often used this prophylactic treatment. During the four years of his illness, he had noticed a gradual change in his gait, and his friends had commented on his stiffness and slowness. He had also noticed a tendency to an increased respiratory rate, which occurred only on exercise.

The general examination was essentially negative, except for evidence of Parkinson's disease with the usual gait, facies, and muscular rigidity. There was slight hypertension (130 systolic and 100 diastolic), and rather striking peripheral arteriosclerosis for so young a man. The laboratory examinations, including blood count, blood Wassermann tests, the basal metabolic rate, and roentgenograms of the head, were negative. The output of urine varied from 8 to 13 liters in twenty-four hours. The intake was correspondingly large, but on two occasions exceeded the daily output by 4 and 6 liters respectively. The fluctuations of the fluid intake and the corresponding changes in body weight were striking, and at once recalled to mind similar changes noted in Case 1. Examinations of the urine were repeatedly negative, except for low specific gravity. While the patient was under observation, pituitrin and "vasopressin" were both given without effect on either the thirst or polyuria. Cocainization of the throat did not have any effect on the thirst and the patient resented any attempts to restrict the fluid intake.

During the whole period of observation, the patient's extremities were cold and cyanotic, a point which he had observed himself and correctly attributed to the large intake of fluid. Before his dismissal from the hospital, a final attempt was made to control symptoms by the use of "vasopressin"; two doses of 1 c.c. were given during the course of the day with a decrease of polyuria of 4 liters. The thirst, however, continued unabated and during the time when the vasopressin might have been supposed to be acting, the patient drank about 8 liters of water while voiding less than 2 liters of urine. During the day he became extremely excitable and disoriented with a coarse tremor and every evidence of nervous stimulation. Within a short time, he had a single epileptiform convulsion, which came on without warning; it was not accompanied by foaming at the mouth or loss of sphincter control. The respiration was slow and stertorous; the pupils were dilated and the face flushed. He was unconscious for about five minutes and recovered spontaneously. For about half an hour afterward, mental confusion and muscular incoördination occurred.

A diagnosis of Parkinson's syndrome with secondary epidemic enceph-

alitis, diabetes insipidus, and water intoxication was made, and the patient was dismissed with a warning as to the necessity of keeping the intake of fluid under the strictest possible control.

Case 3.—A schoolboy aged fourteen years was brought to the clinic October 26, 1927. He had had influenza in February, 1925, followed by a period of extreme restlessness and irritability, which lasted until the middle of the summer. A year later, increased thirst and appetite developed, and he began to void large quantities of urine. The polyuria became steadily worse and at the time of examination he was voiding about thirty-six times in twenty-four hours, with enuresis occasionally during the first part of the night. He had also suffered from digestive disturbances and vomiting, probably because of rapid eating and drinking. Stools had been loose and frequent at times, possibly from the same cause.

General examination disclosed the definite syndrome of Parkinson's disease. The muscles were moderately rigid; the face was expressionless and there was a course tremor of the extremities. There was a suggestive pallor of the optic disks. The extremities were cold and cyanotic and the skin was mottled with bluish spots. During the patient's short stay in the examining room he drank fifteen cups of water and voided large quantities of urine. He was hospitalized immediately for study with a tentative diagnosis of diabetes insipidus due to epidemic encephalitis.

In the hospital, the intake of fluid and the output varied within wide limits. On careful restriction of fluids, the patient could manage with about a 4-liter fluid exchange. On some occasions he drank as much as 26 liters of water and voided 16 liters of urine, a tremendous amount for a boy weighing only 90 pounds. The urine was always of low specific gravity, but otherwise was normal. The blood count, blood Wassermann reaction, and the examination of the spinal fluid were entirely negative.

After a few days' observation, 0.5 c.c. of pituitrin (surgical) was given hypodermically. This controlled the polyuria somewhat, but the thirst was unabated and within a little less than nine hours the intake had exceeded the output by more than 3 liters. Nine thousand cubic centimeters of water had been taken during this period, according to the nurse's record, and probably even more had been taken since the child was ambulatory and had access to drinking water. Six hours after the pituitrin was given, while the patient was up and about, asking for water, he fell to the floor in a generalized convulsion, which lasted about two and a half minutes. He was put to bed and immediately vomited a large quantity of water and undigested food. Following this, he was stuporous and rigid; thirty-five minutes later he had a second generalized convulsion, which lasted only about ninety seconds. During the next two hours he had four more slight convulsions. Later in the evening he became quiet and slept well throughout the night. Three days later pituitrin was again given, with almost identical results. The polyuria was controlled somewhat, but the thirst was apparently not affected. During the evening he became drowsy and had a number of attacks which were not distinguishable from petit mal. Two days later these attacks were again observed. The patient had not had pituitrin on this day, but was still drinking

large quantities of water. An attempt was made to control the fluid intake by disciplinary measures, with fairly good success, through the coöperation of the parents. The rest of the patient's stay in the hospital was uneventful and he was dismissed four days later. Phenobarbital was prescribed and a course of sodium cacodylate was suggested.

The final diagnosis was epidemic encephalitis, Parkinson's disease, diabetes insipidus and possibly water intoxication. It is noteworthy that this patient had never had convulsions previously.

COMMENT

It will be noted that each of these three patients had suffered from epidemic encephalitis, and had, at the time of their examination, the familiar Parkinson's syndrome. Each of them had also definite signs of mental deterioration and defect of judgment; each suffered from a sort of compulsion thirst, which seemed to be practically uncontrollable at times, and each persisted in consuming great quantities of water in spite of attempted surveillance and disciplinary measures. It is also noteworthy that the convulsive seizures either followed tremendous bouts of water drinking, or after pituitrin had reduced the urinary output somewhat. So far as I know, these phenomena have never been observed in diabetes insipidus due to any other lesion; one is struck with the possibility that there may be some inherent peculiarities in diabetes insipidus secondary to epidemic encephalitis, which render the affected individual particularly susceptible to water intoxication.

Twenty-three patients with diabetes insipidus were observed at The Mayo Clinic from January 1, 1924 to January 1, 1929. Nine of these had the primary or so-called idiopathic type of the disease, one had associated meningeal and vascular syphilis, two had pituitary tumors, in one the condition was questionably related to trauma, one had associated progressive lenticular degeneration, and one had polyglandular deficiency with eunuchoidism.

The condition in the remaining eight patients was presumably secondary to encephalitis. Six patients had the definite facies, muscular hypertonicity, tremor, and the gait of the parkinsonian state; one patient had questionable recent encephalitis with striking mental deterioration and tremor, and

the eighth patient did not have objective neurologic symptoms but gave a suggestive history pointing to previous encephalitis (Tabulation).

SUMMARY OF DATA IN SEVEN CASES OF DIABETES INSIPIDUS WITH OBJECTIVE NEUROLOGIC SIGNS

Sex and age.	Duration of polyuria, years.	Variation in intake of fluid, c.c.	Variation in output of urine, c.c.	Effect of pituitrin on polyuria.	Comment.
M. 19	1.2	8,160 26,380	6,650 25,500	Absent.	Marked personality changes and frequent periods of stupor which may have been water intoxication.
M. 27	4	10,000 28,400	10,000 26,000	Slight; variable.	Water intoxication.
M. 23	4	8,000 14,000	8,000 12,400	Practically, absent.	Water intoxication.
M. 22	3	3,000 6,660	3,000 9,600	Practically, absent.	Respiratory syndrome following encephalitis.
M. 16	4	6,600 31,700	3,750 28,940	Slight.	Could control thirst by voluntary effort.
M. 16	4	6,000 15,840	3,200 14,000	Moderate.	Could be held under fair control with pituitrin.
M. 14	2.5	3,300 25,850	8,700 16,000	Slight.	Water intoxication.

This group of seven patients with objective evidence of encephalitis was composed exclusively of young male patients, in whom polyuria had been present for one to four years. The diabetes insipidus in these individuals differed from that usually observed in the extreme variability of intake and output and in the response to treatment with pituitrin. In only one of the group was the thirst materially affected by the use of pituitary extracts, when administered hypodermically, orally, or intranasally. In one case the polyuria was not at all affected; in the other six cases it was affected slightly and to a variable degree, large doses being required to produce any appreciable reduction in the output of urine. In the three cases which I have described a study of the fluid balance and weight curves showed remarkable fluctuations, indicating periods of water storage and water loss; none of these had suffered from convulsive seizures previously nor did they come from epileptic

families. It is well recognized that grand and petit mal are rarely encountered in association with the residues of encephalitis, although it is possible the individuals with postencephalitic parkinsonism may have heightened cortical irritability and an increased susceptibility to convulsions from toxic causes.

Although practically all of the patients suffering from postencephalitic diabetes insipidus who have been observed at The Mayo Clinic have taken a large amount of fluids, only four have had a really uncontrollable thirst. Since all of these manifested striking personality changes and defects of judgment it is easy to see how water intoxication might develop, particularly when the urinary output was reduced by pituitrin. Three of the four patients had definite convulsions under these circumstances; the fourth patient had periods of stupor and coma, which in retrospect may well be considered to have been due to water intoxication. It is true that the amount of fluid taken by these three patients was somewhat less than that required to produce water intoxication in the experimental animal. However, the degree of dilution of blood and waterlogging of tissues required to produce the condition in patients may not be the same as that required for experimental animals; also, the patients in question suffered from the handicap of gross cerebral injury.

The nature of the compulsion thirst in such patients is of much interest from the standpoint of experimental pathology. Curtis has shown that injury to the hypothalamic cortex in dogs will produce temporary experimental diabetes insipidus in which thirst is the primary phenomenon. Bourquin recently stated that diabetes insipidus is in reality an irritation phenomenon, the central lesion causing excessive production of a diuretic substance. She found that after injury to the mammillary bodies in the dog much larger quantities of this diuretic substance could be extracted from the midbrain than from the same region in control animals. However, diabetes insipidus is a syndrome secondary to a wide variety of lesions; Fink, in a recent article described a group of cases implicating every part of the base of the brain and pituitary gland. It is reasonable to suppose that

with certain lesions the thirst may be primary, and that with others, the polyuria may appear first. Curtis believes that: "It is as reasonable to regard experimental diabetes insipidus as an hypothalamic thirst phenomenon as to regard it as being a primary polyuria." In the three cases of water intoxication presented here, there was strong evidence to show that the thirst antedated the polyuria; it would be overstating the case to say that this is the rule in all cases of diabetes insipidus secondary to encephalitis, although a study of the fluid balance in these cases inclines one to this view.

SUMMARY

Postencephalitic diabetes insipidus differs from that due to other lesions in the variability of intake and output and in the therapeutic response to pituitrin. In certain cases, a compulsion thirst may exist which may amount almost to mania for water; this thirst, when existing in patients with defective judgment, may lead to the consumption of enormous quantities of fluid. If their fluid intake is unrestricted or if the output of urine is reduced by pituitrin, there may be episodes indistinguishable from experimental water intoxication in animals. In such cases the necessity for caution in the use of pituitrin and for the adoption of every possible measure to curb excessive intake of fluid is obvious.

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INSULIN RESISTANCE IN A CASE OF BRONZE DIABETES

FRANK N. ALLAN AND GEORGE R. CONSTAM

WHEN insulin was first introduced everyone agreed that it was specific in all cases of diabetes. Even the most severe diabetes was successfully controlled. Although certain cases under the influence of toxemia, acidosis, and hyperthyroidism presented more than usual difficulty, they responded to intensive treatment. The consistent action of insulin was considered to be not only a therapeutic triumph but a vindication of the pancreatic theory regarding the etiology of the disease. According to F. M. Allen and Sherrill, "The unity of diabetes is now further established and diabetes is scientifically definable only as deficiency of the internal secretion of the pancreas."

During the last few years experience has accumulated which may necessitate a change of opinion regarding the uniform behavior of insulin. Cases have been reported which were relatively refractory. An example of extreme insulin resistance has recently been observed in a case of bronze diabetes described here.

REPORT OF A CASE

A man aged fifty-eight years a bond salesman, came to The Mayo Clinic in April, 1928. In 1903, bronchial asthma induced him to move from New York to Oklahoma where he found complete relief. In 1908 he suffered from an attack of malaria. For the last six years he had, off and on, experienced severe cramps in the legs, especially at night. Heat eased the cramps and arch supports gave temporary relief. In the autumn of 1926, after an attack of bronchitis, his strength began to fail. Definite symptoms of diabetes, such as blurring of vision, polydipsia and polyuria, developed in September, 1927. The following month he consulted a physician, an oculist, who advised dental extractions. The dentist, however, insisted on a general examination and thus glycosuria was discovered. At first diabetes was treated by means of diet alone, but soon the use of insulin became necessary. The dosage had to be increased steadily. Six days prior to admission, acidosis had developed, and large doses of insulin, up to 300 units in one day, were required.

The patient weighed 103 pounds. His skin was dry and dark grayish-brown, with a metallic glitter, especially on the exposed parts and in the anogenital region. The skin had always been dark, but had become more pigmented during the last year. The mucous membranes were free from pigmentation. The systolic blood pressure was 100 mm. mercury, the diastolic 64. There was an odor of acetone on the breath. The edge of the liver was palpable 3 cm. below the costal margin in the right midclavicular line; the spleen could not be felt. There were scoliosis of the dorsolumbar

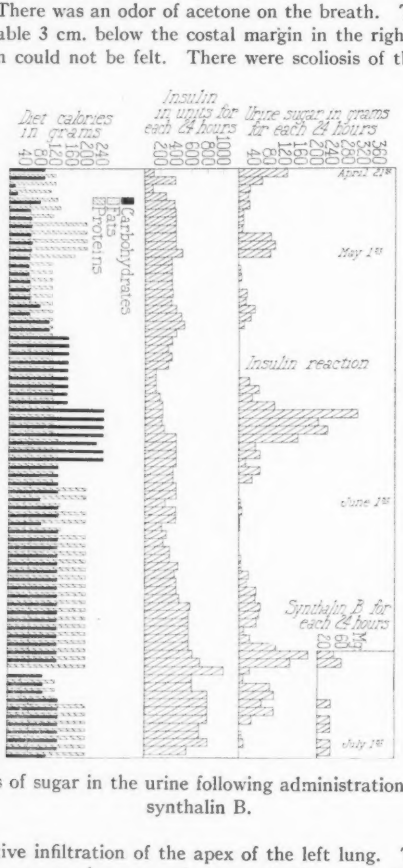

Fig. 269.—Loss of sugar in the urine following administration of insulin and synthalin B.

spine and inactive infiltration of the apex of the left lung. The urine contained a large amount of sugar and acetone bodies. The blood contained 325 mg. of sugar and 61 mg. of urea for each 100 c.c. The carbon dioxid combining power of the plasma was 26 volumes per cent. The van den Bergh reaction was direct; the serum bilirubin was 1.6 mg. for each 100 c.c. The values for serum calcium and phosphorus, for blood fats and cholesterol, for nonprotein nitrogen and amino acid nitrogen are given in the tabulation.

There was slight secondary anemia (hemoglobin 72 per cent, Dare, and 3,400,000 erythrocytes). The blood Wassermann reaction was negative. A roentgenogram of the chest did not show any pathologic change. Cells carrying hemosiderin were found in the urinary sediment. This is a sign of hemosiderosis of the kidneys, a condition met not only in hemochromatosis, but also in other diseases, such as pernicious anemia and malaria.[25] Copper was not found in the urine. A section of the skin revealed the presence of hemosiderin around the sweat glands, which is typical of hemochromatosis.

A diagnosis was made of hemochromatosis (bronze diabetes) with acidosis. Addison's disease was considered in the differential diagnosis, particularly since histologic examination of the skin showed an increase also of melanin. Clinically, however, the picture was not that of Addison's disease. Asthenia was not marked after treatment of acidosis. The systolic blood pressure varied between 95 and 122, usually above 100. The mucous membranes were not pigmented, although this has been noted in a few proved cases of hemochromatosis.[3, 5, 26, 30] Metal poisoning, such as argyria or arsenic melanosis, was ruled out from the history.

Treatment for diabetic acidosis was begun. Although 130 units of insulin were given during the first twenty-four hours, the blood sugar was higher on the second day, and the clinical symptoms of acidosis were more marked. More than 300 units were necessary to reduce the hyperglycemia. The administration of large doses of insulin was continued. Acidosis was checked, and the patient's condition improved. Several hundred units of insulin daily were at first not sufficient to control glycosuria. After the dosage was increased to 480 units a day, the urine became almost sugar-free on the twelfth day after admission, and was entirely sugar-free after 500 units on the twenty-first day (Fig. 269). The insulin requirement remained elevated, and fluctuations in carbohydrate tolerance made adjustment of the dosage of insulin extremely difficult. With the help of frequent analyses of urine and blood, insulin reactions were avoided with one exception. On this occasion symptoms of hypoglycemia were mild and were promptly relieved by the ingestion of sugar. It was impossible to control glycosuria continuously for more than a few days, yet the patient began to regain his health gradually. His strength improved, and his weight increased.

Various dietary measures were tried in succession in the hope of facilitating treatment. A diet low in carbohydrate and protein with a relatively high allowance of fat was not satisfactory since only part of the glucose was utilized and ketosis developed. With a high carbohydrate diet the difficulty in controlling glycosuria was increased. A diet with moderate restriction of carbohydrate and protein was finally adopted. The administration of insulin in many small doses seemed to be less effective than the administration of three or four large doses. Intravenous injection apparently hastened its action, but the total effect was about the same. Treatment with sodium bicarbonate did not have any effect on the insulin requirement.

Several weeks after admission, acute respiratory infection developed, and at this time ascites appeared with the accumulation of a small amount of fluid in the left side of the chest. Enlarged veins, an indication of collateral circulation, were observed in the abdominal wall. Recovery from the

respiratory infection took place in eight days, and the patient regained his strength, although some degree of ascites remained. A month later, treatment with synthalin B was commenced, being used with great caution because of the fear of a possible toxic action on the diseased liver. Only a few doses were given before a fatal complication developed and, therefore, definite conclusions cannot be drawn as to the effectiveness of the drug in this case.

About three months after admission the patient was seized suddenly with intense abdominal cramps and nausea and vomiting. He had been feeling well the evening before, the urine being free of sugar and the blood sugar about normal. The abdominal pains continued and extreme prostration developed. Death occurred within twenty-four hours of the onset of these symptoms.

Postmortem examination revealed general peritonitis of cryptogenic origin. The typical manifestations of hemochromatosis were found in marked cirrhosis of the liver, and fibrosis and atrophy of the pancreas. The islands as well as the acinous tissue were partly replaced by fibrous tissue. The suprarenal glands appeared normal except for hemosiderosis of the cortex. Small areas of bronchopneumonia were noted in the lungs, and the aortic valves showed signs of recent endocarditis. The coronary arteries were markedly sclerosed. The testicles were not atrophic. The liver was found to contain nearly 0.62 per cent of iron.

COMMENT

Bronze diabetes is a curious disease which has aroused considerable interest among clinicians and pathologists during the last sixty years. Trousseau, in 1870, described a case of diabetes with enlargement of the liver and bronze pigmentation of the skin. Troisier, in 1871, at a meeting of the Anatomical Society of Paris, demonstrated the organs of a diabetic patient with pigmented skin. Chauffard and Hanot were the first to describe the clinical entity of "diabète bronzé" and its diagnostic triad, pigmentation, cirrhosis, and glycosuria. The condition was regarded as ordinary diabetes with some unusual features until von Recklinghausen discovered the two characteristic pigments, hemofuscin and hemosiderin, and described as hemochromatosis the more general condition underlying bronze diabetes.

Hemochromatosis usually affects patients in the fifth and sixth decades although it has been observed in patients aged twenty-eight and seventy-three years. It generally occurs in men. Its onset is insidious. Pigmentation usually develops before cirrhosis of the liver becomes apparent, and glycosuria

comes on still later. Not all cases, however, follow this rule. The combination of the typical pigmentation with cirrhosis of the liver or with diabetes is considered sufficient evidence for the clinical diagnosis of hemochromatosis. Cases in which there is pigment cirrhosis and diabetes, without pigmentation of the skin, are correctly diagnosed only at necropsy.

Pathologically hemochromatosis is characterized by a deposit of the typical pigments in the skin and in almost all the viscera, by cirrhosis of the liver, and fibrosis of the pancreas. Histologically, at least two pigments can be found, both derived from hemoglobin: hemosiderin which contains iron, and hemofuscin which is iron-free. Both pigments, hemosiderin preponderantly, are present in the parenchymatous and connective-tissue cells, and there is mainly hemofuscin in the smooth muscle cells of the intestine, the lymphatics and the blood vessels. Frequently the normal pigment of the skin, melanin, is also increased, as in Addison's disease.

The etiology of hemochromatosis is unknown. As in the case of most obscure diseases, its cause has been attributed to alcoholism, syphilis, and intestinal intoxication. Mallory was able to produce experimentally changes like hemochromatosis in rabbits, monkeys, and sheep by prolonged administration of copper acetate. He believed the disease in human beings to be due to slowly acting copper intoxication. In sixteen of a series of nineteen cases he was able to trace a possible source of exposure to copper. The patients had worked in a brass mill, or they had used liquors excessively which presumably had been contaminated with copper from the worm of the condenser in distillation, or they had used acid food or beverages that had been cooked in copper vessels. The clinical proof of his contention is uncertain. As adverse evidence it may be noted that an increase in the copper content of the liver or other organs has not been found, and copper has not been demonstrated in the excreta. In Koreans who are presumably exposed to copper by the habitual use of brass vessels in cooking and eating, Mills did not find cases of hemochromatosis.

Diabetes is often a late manifestation of hemochromatosis.

The carbohydrate tolerance is sometimes subject to marked fluctuations, glycosuria, therefore, being intermittent. On account of this, and because some cases do not show changes in the pancreas, certain authorities, including Naunyn and von Jaksch, have considered such diabetes to be of hepatic origin. In hemochromatosis, however, there is often histologic evidence of extensive alteration in the islands of Langerhans. Anschütz reported a case of hemochromatosis with simultaneous disturbance of the external secretory function of the pancreas. Although the primary cause of diabetes in these cases undoubtedly lies in the pancreas the manifestations of the disease may be modified by the associated hepatic disorder. Decided change in the tolerance of diabetic patients with cirrhosis or hepatic tumor corresponding to the change in tolerance described in cases of bronze diabetes has been reported by Hoffmann and by Wilder. These observations agree with the experience of Mann and Magath in the removal of pancreas and liver from a dog.

The diabetes of hemochromatosis is usually severe, and in the past most patients have died from coma within a few months or a year after the onset of glycosuria. The discovery of insulin has modified the prognosis. With the exception of the case reported here, the cases of hemochromatosis observed at The Mayo Clinic since insulin has been available, have responded to treatment in the usual way, and the disturbance in carbohydrate metabolism has been controlled without difficulty. The unusual course of diabetes in this patient, and the exceptional behavior under insulin treatment made his existence precarious, yet the fatal termination was due to the occurrence of a complication. Certain patients are able to maintain good health if diabetes is controlled. One of our patients who was found to have hemochromatosis five years ago is today strong and vigorous, so that he carries on the active work of a railroad baggage man. The hepatic disorder which frequently results in ascites is now the most serious menace in these cases.

Reports of the treatment of bronze diabetes with insulin have been published from various sources.[3, 6, 8, 16, 26, 29, 30, 32] As a rule insulin has been effective in controlling glycosuria,

although treatment in certain cases was difficult because of the severity of diabetes, or because of other peculiarities such as instability of the blood sugar level.

True insulin resistance is rare not only for hemochromatosis, but for diabetes of any type. Yet an increasing number of cases which have been refractory to insulin in some degree has been observed. In some cases the refractory state has lasted for only a few weeks or a few months. There has not been absolute failure of insulin to act, but the amount required has been from two to five times the maximal amount used for the usual case of severest or "total" diabetes. Only two cases on record appear to have shown such extreme resistance to insulin action as was exhibited by the case reported here. One such patient, described by Joslin, had diabetes complicated by cirrhosis of the liver. He required an increasing dosage of insulin, and eventually needed 850 units daily. Two days before his death in coma he received 1,600 units in twenty-four hours. The other case was reported by Glassberg, Somogyi, and Taussig, who reviewed the previous reports and discussed the theoretic considerations in detail. Their case, for a period of several months responded only to enormous doses of insulin; an average of 317 units was given each day for nearly three months. Later the response to insulin increased and the case again became one of ordinary, moderately severe diabetes. A case in which 250 units were required daily, described by Lawrence, differs from the others in that the blood sugar was lowest after a night's fast, and when the patient was starved his blood sugar fell spontaneously, instead of rising, as is usual in severe diabetes when insulin is withheld. Yater described a case seen at The Mayo Clinic in which the patient with diabetes and acromegaly failed to respond after thyroidectomy to large doses of insulin amounting to 215 units in one day.

Several hypotheses have been advanced to explain the condition. Since cirrhosis of the liver is one of the prominent features of bronze diabetes, it is natural to assume, in this case, that the resistance to insulin depended on some disturbance of hepatic function. In the insulin-resistant case, described by

Joslin, cirrhosis was also present. One would expect, however, that loss of hepatic function would have the opposite effect, since removal of the liver is followed by fall in blood sugar. In an attempt to explain the association of the disorder of the liver and insulin resistance one might employ Loewi's hypothesis that the liver produces a secretion, "glykamin," which acts as an antagonist to insulin. According to Loewi's view, diabetes may be due either to lack of insulin or to excess of glykamin. In the case reported here the diseased liver might have been producing an abnormally large amount of glykamin. In other cases refractory to insulin, signs of disease of the liver have not been present, and here there was nothing to indicate that the resistance to insulin was related either to the hemochromatosis or to the cirrhosis of the liver. The patient observed by Glassberg, Somogyi, and Taussig showed signs of allergy, and it was suspected that insulin might have been destroyed or inactivated by some anaphylactic process. Since our patient had suffered from bronchial asthma he may have been allergic and the same explanation might be applicable here. Another theory is that there is lack of some substance which acts like a co-enzyme with insulin in the utilization of carbohydrate. Evidence of the existence of such a substance has been put forth by several investigators. Ahlgren has named it "glycomutin"; Lundsgaard and his associates call it "insulin complement," and Brugsch and Horsters claim that it is a "phosphatese," concerned with the synthesis of hexosephosphate as a preliminary step in carbohydrate metabolism. Häusler and Högler as a result of studies of the effect of insulin on the absorption of sugar by erythrocytes concluded that the condition of insulin resistance is due to the inaccessibility of the body cells to the action of insulin.

Unfortunately our efforts to solve the problem, like those of other workers, have not been successful. Experiments performed according to Loewi's technic, for the purpose of demonstrating an excess of glykamin in the blood, were inconclusive. Furthermore, the mixture of the patient's serum with insulin did not affect the fall in blood sugar when it was injected into a rabbit. This, of course, does not disprove the presence of anti-

insulin since the amount contained in a relatively small volume of serum might be ineffective. Whether insulin-refractory diabetes is due to the presence of anti-insulin, or to the absence of insulin complement or to some other cause, has not been decided.

Although the condition is rare, the reporting of such a case as the foregoing is of value, not because it illustrates a metabolic curiosity, but because it presents important theoretic and practical considerations. From the theoretic standpoint the occurrence of such cases supports the view that diabetes may depend on factors other than pancreatic insufficiency alone. From the practical standpoint it is essential to recognize that cases refractory to insulin exist, so that patients may not be permitted to die needlessly or prematurely because they do not receive a sufficient amount of insulin

ANALYSIS OF BLOOD ON THE PATIENT'S ADMISSION TO HOSPITAL

	Amount, mg. per cent.	Normal, mg. per cent.
Sugar	350	80–120
Urea	61	20– 40
Creatinin	1.2	1– 3
Uric acid	3.8	1– 4
Amino acid nitrogen	7.4	5– 7
Van den Bergh reaction	direct	indirect
Serum bilirubin	1.6	
Calcium	8.6	9– 11
Phosphorus	4.6	2– 5
Carbon dioxid combining power of plasma	26 volumes per cent	55– 70 volumes per cent

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PULMONARY ARTERIOSCLEROSIS*

WALLACE M. YATER AND GEORGE R. CONSTAM

SCLEROSIS of the pulmonary artery was described as early as 1706 by Vieussens, in 1816 by Kreysig, in 1826 by Louis, in 1829 by Andral, in 1835 by Bouilland and since then by many others. In 1908 and 1909 Posselt emphasized the clinical as well as the pathologic features of pulmonary arteriosclerosis. Giraux devoted a splendid thesis to this subject in 1910.

In 1901 Abel Ayerza described in a lecture given in his clinic the clinical syndrome of hypertrophy of the right ventricle with cyanosis and polycythemia in persons with chronic pulmonary disorders. From the appearance of the patients he called them "cardiacos negros" or "black cardiacs." In 1912, his pupil, Arrillaga, in a thesis on this subject, stated that arteriosclerosis of the pulmonary vessels secondary to pulmonary disease was the anatomic substratum for this syndrome, and he called it "Ayerza's disease." This opinion was concurred in by Warthin among others, who suggested that the etiology in some cases was syphilis. In 1924, Arrillaga revised his conception of Ayerza's disease, concluding that it is syphilitic sclerosis of the pulmonary arteries with accidental or secondary changes in the pulmonary parenchyma. Escudero modified this conception, making the obliterative sclerosis of the pulmonary artery secondary to bronchial syphilis. None of these theories has been sufficiently substantiated.

From this brief review, it appears that Ayerza's disease is a syndrome the exact causes of which are not definitely known, and since Ayerza was not the first to describe the picture of failure of the right side of the heart with cyanosis secondary to pulmonary disorders† we see no reason to attach his name to

* Work done in the Division of Medicine and the Section on Pathologic Anatomy as fellows in The Mayo Foundation, Rochester, Minnesota.

† In fact Ayerza did not publish an article on this subject until 1925.

it. Ayerza was perhaps the first, however, to emphasize the occurrence of polycythemia. As this is a secondary symptom* due to the compensatory mechanism which acts in all states of simple chronic reduction in pulmonary ventilation, it is scarcely reason to justify the use of Ayerza's name.

PATHOGENESIS

Arteriosclerosis of the pulmonary artery is found in cases with or without arteriosclerosis of the general circulation. The degree of the latter has apparently no influence on the occurrence of the former, as pulmonary arteriosclerosis may be absent in cases of extreme arteriosclerosis of the general circulation. Whether the apparent independence of arteriosclerotic processes in the two circulations is caused by the difference in blood pressure or in the chemical composition of the blood is speculative.

According to most of the writers, two types of pulmonary arteriosclerosis, a primary and a secondary, are to be distinguished. Gamma compared the secondary pulmonary arteriosclerosis, which is principally localized in the large and medium-sized arteries, with the arteriosclerotic kidney, and the primary sclerosis of the small arteries of the pulmonary parenchyma with the kidney in which the arterioles are sclerotic. The sclerosis of the large branches may lead to dilatation of the lumen, while the disease of the small vessels produces obstruction of the circulation through hypertrophy of the media. Most of the authors considered the involvement of the arterioles as a manifestation of arteriosclerosis, but Schütte regarded it as a specific vascular disease of unknown origin.

Primary pulmonary arteriosclerosis causes very marked hypertrophy and dilatation of the right side of the heart. The valves are normal and the left ventricle usually is not enlarged. The trunk of the pulmonary artery frequently is dilated, but it does not necessarily contain sclerotic areas. The parenchyma of the lungs and the pleura usually are unaltered. This type of pulmonary vascular disease is very rare.

* In spite of Kitamura who attributed pulmonary arteriosclerosis in heavy beer drinkers to their increased blood content.

Pulmonary arteriosclerosis is not uncommon as a secondary manifestation of numerous conditions, usually cardiac or pulmonary. In such cases the main involvement is either in the larger branches of the pulmonary arterial tree or in the capillaries in the alveolar walls, manifesting itself in the latter as an arteriocapillary thickening. Mitral stenosis apparently is the most common agent in producing the latter lesion and pulmonary emphysema of the essential type has also been regarded as a causal factor. We are not in a position at the present time to give our own impression regarding the capillary changes in essential emphysema. But in a series of cases which we have studied, the arterioles were unaffected, and the changes in the arteries of the second and third degree were only those which are observed in the lungs of individuals of the same age. In this view we are supported by Runeberg and Saune, but Fischer found evidence of sclerosis of the pulmonary arterioles in all cases of emphysema. Arrillaga and also Eymery considered that when emphysema or other pulmonary lesions were found in cases of pulmonary vascular disease, such lesions were accidental or secondary to the vascular changes; in other words, they did not believe pulmonary arteriosclerosis was ever secondary to parenchymatous pulmonary disease. Pulmonary arteriosclerosis may be observed at necropsy in any case in which marked reduction of volume of the lung had existed, such as results from tuberculosis, chronic interstitial pneumonia, and neoplasms of the lung and mediastinum. It is also seen in cases of congenital heart disease, such as patent foramen ovale, patent interventricular septum, and patent ductus arteriosus.

CLINICAL MANIFESTATIONS

The clinical manifestations of pulmonary arteriosclerosis are due to impaired gas exchange in the lungs and hypertension in the lesser circulation. The outstanding clinical symptom is cyanosis, which for a long time is quite out of proportion to the dyspnea and other signs of passive congestion. In primary pulmonary arteriosclerosis the left atrium and the pulmonary veins do not appear to be enlarged on fluoroscopic examination. The

widening of the pulmonary artery (left middle arch in the skiagram) is present in the majority of cases. The hypertrophy of the right ventricle and the right atrium is characteristic. The second sound in the pulmonic area is accentuated and a diastolic murmur is heard in rare cases over the pulmonary ostium without signs of valvular insufficiency. A thrill has been observed in the region of the pulmonary valve. Increase in the number of erythrocytes, of hemoglobin, of blood volume, and viscosity, right ventricular preponderance in the electrocardiographic tracing, and lack of response to digitalis, complete the clinical picture. In sclerosis secondary to an affection of the left side of the heart not only the pulmonary artery but also the pulmonary veins, and the left atrium are enlarged, and according to Eppinger the transparency of the lung fields is decreased. Posselt described, in pulmonary arteriosclerosis secondary to mitral stenosis, a zone of dulness to the left of the upper part of the sternum with some tenderness on pressure and percussion in the same area. He also observed gradual progression of the diastolic murmur and thrill from the apex toward the pulmonary ostium. As "dyspragia intermittens angiosclerotica pulmonalis" Posselt described attacks of pain in the region of the base of the heart associated with deepening cyanosis. In the two cases reported here, in which sclerosis of the pulmonary arterioles was found, one may speculate as to the various relationships of the coexisting lesions in each.

REPORT OF CASES

Case 1.—A coal miner aged fifty-one years came to The Mayo Clinic complaining of dyspnea, edema of the legs, and burning pain in the epigastrium. He had been perfectly well until nine years previous to his last examination. At that time he had had influenza followed by pneumonia. Since then he had been suffering from dyspnea on exertion, which had been so bad in the last four years that he had been unable to work. If he slept on his back, as had previously been his custom, he was awakened by choking spells. Consequently he formed the habit of lying on his abdomen during rest. Two years before registration at the clinic he had had one attack of hemoptysis. During the six months prior to registration edema had developed in the ankles and had gradually spread toward the knees. During this period he had suffered from nocturnal attacks of precordial pain. Gallstones had been removed surgically five years previously after several attacks of colic

associated with jaundice. Some bloating, belching, and occasional attacks of burning epigastric pain had become more bothersome during six months prior to his examination.

On admission the patient weighed 140 pounds. Dyspnea and cyanosis were marked. There was considerable edema of the lower extremities and of the abdominal wall. The finger tips were clubbed. The upper part of the right side of the chest appeared to be retracted and the breath sounds in the region of the right apex were roughened and prolonged, especially during expiration; in the remainder of the lung the breath sounds were distant. Coarse, moist râles could be heard scattered throughout the entire chest.

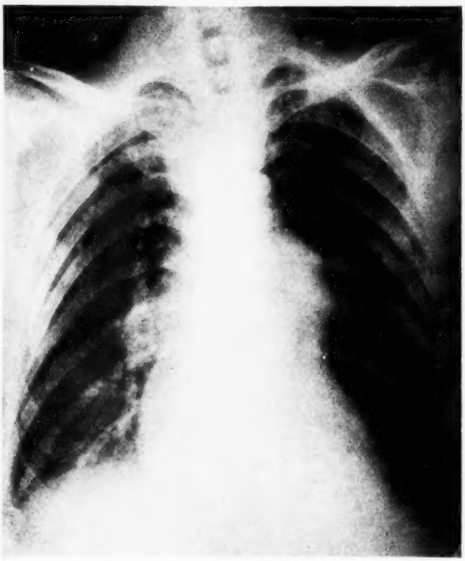

Fig. 270.—(Case 1.) Enlargement of the right ventricle and of the left middle arch of the cardiac shadow.

There was evidence of the presence of a moderate amount of free fluid in the left pleural cavity. The liver dulness extended 3 cm. below the right costal margin. The temperature was normal. The blood pressure was 120 systolic and 80 diastolic; the pulse rate was 80 and the heart action regular. The left border of the heart did not extend beyond the left midclavicular line, and the right border was percussed 2.5 cm. to the right of the sternum. There was a rumbling first sound with a tendency to reduplication at the apex. The second sound had a snapping quality. A roentgenogram of the chest showed hypertrophy of the right ventricle, and enlargement of the heart through the region of the right atrium and the left middle arch (Fig. 270). The paren-

chyma of the lung did not show definite involvement, except perhaps evidence of passive congestion at the bases. The hemoglobin estimated by the Dare method was 98 per cent (normal, 75), the erythrocytes numbered 5,680,000 in each cubic millimeter, and the leukocytes numbered 5,600 in each cubic millimeter. A Wassermann test of the blood was negative. The urine was of normal specific gravity and contained a trace of albumin with a few hyaline casts. The blood urea was 32 mg. in each 100 c.c. of blood. An electrocardiogram revealed slight slurring of the QRS complex in leads I and II, notching of the QRS complex in lead III, and right ventricular preponderance. Acid-fast bacilli could not be found in the sputum. The retinal arteries showed some evidence of fibrosis on ophthalmoscopic examination.

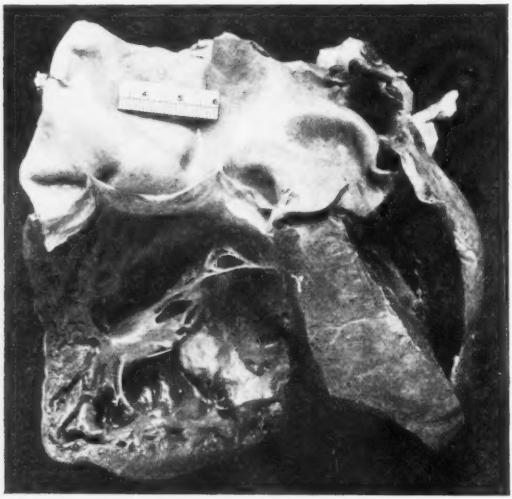

Fig. 271.—(Case 1.) The opened heart, showing the hypertrophy of the right ventricle and the anterior papillary muscle, and the marked dilatation of the root of the somewhat sclerotic pulmonary artery.

The patient did not respond to digitalis, the cardiac decompensation became progressively worse and death occurred from heart failure twenty-three days after admission.

A necropsy was performed and the pathologic-anatomic diagnosis was as follows: (1) Dilatation and hypertrophy of the right ventricle graded 3 with dilatation, graded 3, and sclerosis graded 2 of the pulmonary artery; (2) chronic mitral endocarditis, graded 1, without apparent stenosis; (3) chronic passive congestion of the liver with atrophy, and atrophy of the spleen; weight of liver 1,205 gm.; weight of spleen, 42 gm.; ascites to the extent of 2,000 c.c.; hydrothorax designated as 800 c.c. on the right and 500 c.c. on the left; anasarca, and edema of the lungs; (5) bilateral emphysema probably

of the essential type, and bronchiectasis with acute terminal bronchitis; (6) evidence of healed tuberculosis in the lungs, and lymph nodes of the hilum with pleural adhesions; (7) pulmonary anthracosis graded 3; (8) arteriosclerosis of the coronary arteries graded 2, of the aorta, graded 2 with mural thrombosis in the abdominal portion; and (9) acute diffuse nephritis.

The heart and lungs attracted most attention and received the most careful study. The heart weighed 420 gm.; its muscle was dark brown and

Fig. 272.—(Case 1.) Gross section of one of the lungs, showing marked dilatation of the somewhat sclerotic pulmonary artery and the anthracosis.

rather flabby and there was no evidence of abnormal fibrosis. The right ventricle was markedly hypertrophied and dilated, while the left ventricle was of normal size (Fig. 271). The chronic endocarditis of the mitral valve was mild and apparently did not cause functional or organic disturbance. The coronary sclerosis was of moderate degree without constriction of the lumens. The pulmonary artery was markedly dilated and showed numerous yellowish plagues, although the wall as a whole was diminished in thickness.

The larger branches of the pulmonary artery were similar to the main artery (Fig. 272). The circumference of the pulmonary artery at its orifice was 10.4 cm. (normal 7.5 cm.). The pulmonary veins appeared normal. The thickness of the wall of the right ventricle was 1.2 cm. (normal, 0.3 cm.). Microscopic sections of the heart muscle revealed only a moderate amount of lipochromatic pigment and diffuse fine fat droplets.

The lungs were voluminous and very dark, due to anthracosis; the cut section was almost black and the alveoli were plainly apparent to the naked eye. The edema was only moderate in amount and the bronchiectasis mentioned was mild. The bronchi were acutely congested. The microscopic examination of the lungs revealed, besides the heavy and extensive deposit

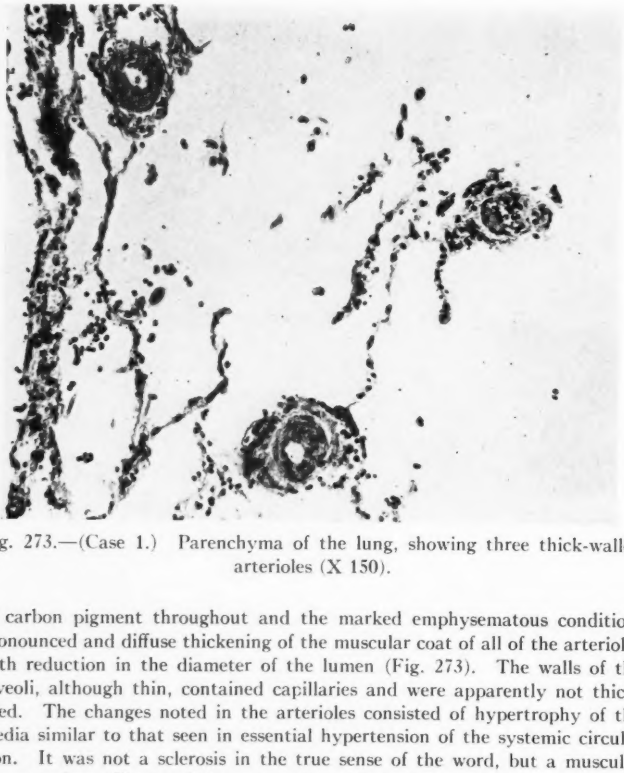

Fig. 273.—(Case 1.) Parenchyma of the lung, showing three thick-walled arterioles (X 150).

of carbon pigment throughout and the marked emphysematous condition, pronounced and diffuse thickening of the muscular coat of all of the arterioles with reduction in the diameter of the lumen (Fig. 273). The walls of the alveoli, although thin, contained capillaries and were apparently not thickened. The changes noted in the arterioles consisted of hypertrophy of the media similar to that seen in essential hypertension of the systemic circulation. It was not a sclerosis in the true sense of the word, but a muscular hypertrophy. The condition was present throughout sections from various parts of both lungs. It was striking because the arterioles, usually thin-walled and inconspicuous, were prominent. The arterioles of the other organs,

on the other hand, did not show hypertrophy or thickening. The diffusely scattered yellowish plaques in the pulmonary artery proved on microscopic examination, to be atheromatous plaques beneath a slightly thickened intima.

Case 2.—A railroad flagman aged fifty-three years appeared for examination complaining of painful swelling of both ankles, dyspnea, and palpitation. His family history was irrelevant. He had been in good health until six to eight months before, when his left ankle became swollen and painful and he began to have dyspnea after slight exertion, with palpitation and some blood-streaked sputum. Later, his right ankle became swollen and painful, similar to the left.

He weighed 147 pounds. He was dyspneic and cyanotic. The fingers were markedly clubbed. The thorax was barrel-shaped and rigid. Percussion of the chest revealed increased resonance over all parts of the lungs except the bases, where moist râles were audible. The heart action was regular. Exact percussion of the heart was impossible because of the emphysema. The first sound at the apex was markedly accentuated, and a blowing presystolic murmur was heard between the apex and xiphoid process. There was severe edema of the lower extremities and the sacral region. The liver could not be felt. The systolic blood pressure was 100 and the diastolic 74; the temperature was normal and the pulse rate was 100. A roentgenogram of the chest revealed infiltration of both upper lobes. The hemoglobin estimated chemically as acid hematin was 21.8 gm. in each 100 c.c. of blood (normal, 15 gm.). The erythrocytes numbered 6,100,000 and the leukocytes numbered 10,800. The total blood volume was determined by the dye method (Congo-red) to be 9,860 c.c. or 148.5 c.c. in each kilogram of body weight (normal, 89 c.c.), with total plasma volume of 2,988 c.c. or 45 c.c. (normal, 50 c.c.) in each kilogram of body weight. The Wassermann test of the blood was negative. The urine contained a trace of albumin. The blood urea was 49 mg. for each 100 c.c. of blood, and the phenolsulphonephthalein test of renal function showed a return of 50 per cent. The electrocardiogram showed right ventricular preponderance and exaggerated P wave in lead II. The diagnosis was rheumatic mitral endocarditis with mitral stenosis, and pulmonary emphysema.

The patient was hospitalized and for a while seemed to improve under treatment with digitalis. Later, however, the auricles began to fibrillate and the patient died suddenly eight days after admission.

The pathologic-anatomic diagnosis in this case was as follows: (1) Chronic mitral endocarditis with stenosis graded 3; (2) hypertrophy of the right ventricle, graded 3 and of the left ventricle, graded 1; (3) chronic passive congestion and atrophy of the liver, which weighed 1,175 gm. and chronic passive congestion of the spleen, which weighed 200 gm.; (4) bilateral essential emphysema of the lungs; in the lungs, there was evidence of old, healed tuberculosis; (5) pleuritis; (6) advanced pulmonary anthracosis; and (7) extreme venous plethora.

The heart weighed 475 gm. The myocardium was firm and of good color. There was a "fishmouth" stenosis of the mitral orifice. The right ventricle was markedly hypertrophied and the left ventricle only slightly hyper-

trophied. The pulmonary artery appeared normal. The aorta showed moderate atheromatous changes.

The lungs were emphysematous and anthracotic. At the apex of the left lung were numerous small, calcareous nodules surrounded by pale, firm tissue. The nodes at the hila were calcareous. Microscopically the lungs were similar to those in Case 1, except that the hypertrophy of the muscular coat of the arterioles was not quite so marked. There was definite hypertrophy of the media of all of the arterioles in sections from various parts of the lungs, however; this was striking and was different from anything we have observed in cases of mitral stenosis (Fig. 274).

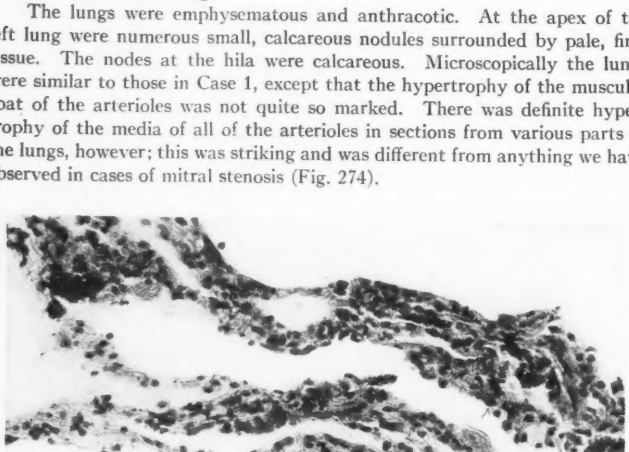

Fig. 274.—(Case 2.) Parenchyma of the lung, showing a thick-walled arteriole (×150).

Comment.—In both cases there was marked sclerosis of the pulmonary arterioles; these vessels resembled those seen in the kidneys in cases of essential hypertension. In Case 1 the pulmonary artery and its large branches were dilated and were somewhat sclerotic. The cases were similar clinically except for the evidence of mitral stenosis in Case 2. Besides the sclerosis of the arterioles of the pulmonary vascular tree, in Case 1 there was marked hypertrophic pulmonary emphysema with anthracosis and in Case 2, besides these conditions, there was marked mitral stenosis.

As yet there is no way of measuring the blood pressure in the pulmonary artery in the human being. However, we may assume from analogy with a like pathologic picture in essential hypertension that in these two cases there was hypertension of the pulmonary circulation. As in essential hypertension of the systemic circulation there is hypertrophy of the left ventricle and often failure of the left side of the heart, so in pulmonary hypertension there would be hypertrophy of the right ventricle and failure of the right side of the heart.

Whether the pulmonary sclerosis of the arteriole was primary or secondary in these two cases is a question. We have stated that this condition is not secondary to essential emphysema or to mitral stenosis. Failure of the right side of the heart in the former condition is supposedly due to a diminution of the pulmonary capillary bed. This effect on the capillaries results from distention of the alveoli and perhaps from arteriocapillary fibrosis following distention and loss of elasticity of the alveolar walls. Mitral stenosis may lead to pulmonary arteriosclerosis, but the involvement is usually arteriocapillary thickening and not sclerosis of the arteriole. Anthracosis does not produce changes in the pulmonary vessels. Our conclusion then is, that the sclerosis of the arteriole in these cases is probably a primary lesion and is not related either as cause or effect to the other existing lesions. In Case 2, although in the mitral stenosis there was sufficient reason for the failure of the right side of the heart, the relative shortness of the course of the decompensation probably was due to a combined strain on the right ventricle. One element of this strain was the pulmonary stasis that followed the mitral stenosis; the other was the pulmonary hypertension resulting from the sclerosis of the arterioles.

In conclusion we wish to emphasize the difference between sclerosis of the main pulmonary artery and its larger branches and the condition of sclerosis of the arterioles. The latter seems to us to be the more important of the two types of involvement of the pulmonary arterial tree. The former may be compared to the decrescent arteriosclerosis of systemic circulation, whereas the latter is similar to the thickening of the arterioles which

occurs in hypertension. These two types of arteriosclerosis are not necessarily associated with each other. In cases in which the large vessels are unaffected, the condition can be recognized only by microscopic examination.

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